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PCT/EP2005/001389
Max-Delbrück-Centrum für Molekulare Medizin
K1577 PCT

Novel pharmaceutical and diagnostic compositions for the treatment and diagnosis of neurodegenerative disorders and amyloid diseases

The present invention relates to pharmaceutical and diagnostic compositions as well as to the use of the active substances contained therein for producing a pharmaceutical or a diagnostic composition for the treatment or diagnosis of neurodegenerative disorders or amyloid diseases.

Various documents are cited in the text of the present description. The disclosure content of the cited documents (including all manufacturer descriptions, information etc.) is herewith incorporated by reference into the present description.

In the prior art, small chemical compounds were identified which can inhibit the aggregation of polyglutamine-containing proteins or amyloid-forming proteins. Patent applications directed to these compounds were filed (Wanker, E. E., Heiser, V., Lehrach, H., Broeker, W., Dunkel, I., Böttcher, H., Barnickel, G., Herhaus, C. (2001) "Inhibitors of PolyQ-Aggregation" EP 01105088.7 and Wanker, E. E., Sittler, A. and Hartl, U. (2001) "Novel compounds useful in the prevention or treatment of diseases associated with protein aggregation and amyloid formation" EP 0110769.5). Excerpts of these inventions and other relevant results were published (Heiser, V., Scherzinger, E., Boeddrich, A., Nordhoff, E., Lurz, R., Schugardt, N., Lehrach, H. and Wanker, E.E. (2000) *Proc Natl Acad Sci U S A. 97*, 6739-6744; Heiser, V., Engemann, S., Brocker, W., Dunkel, I., Boeddrich, A., Waelter, S., Nordhoff, E., Lurz, R., Schugardt, N., Rautenberg, S. *et al.* (2002) *Proc Natl Acad Sci U S A, 99* Suppl 4, 16400-16406 and Sittler, A., Lurz, R., Lueder, G., Priller, J., Hayer-Hartl, M.K., Hartl, F.U., Lehrach, H. and Wanker, E.E. (2001), *Hum Mol* Genet, 10, 1307-1315.).

Other working groups as well described positive effects of chemical compounds on the aggregate formation in Huntington's chorea (Ferrante, R.J., Andreassen, O.A.,

Dedeoglu, A., Ferrante, K.L., Jenkins, B.G., Hersch, S.M. and Beal, M.F. (2002) *J. Neuroscience 22*, 1592-1599, Dedeoglu, A. et al. (2002), *J. Neuroscience 22*, 8942-8950 and Keene, C.D., Rodrigues, C.M.P., Eich, T., Chhabra, M.S., Steer, C.J. and Low, W.C. (2002) *Proc. Natl. Acad. Sci. USA 99*, 10671-10676).

Furthermore, several small molecules were described which inhibit the aggregation of the amyloid ß-peptide relevant for Alzheimer's disease. This includes the following publications: Lashuel, H., Hartley, D.M., Balakhaneh, D., Aggarwal, A., Teichberg, S. and Callaway, D.J.E. (2002), *J. Biol. Chem. 277*, 42881-42890; Merlini, G., Ascari, E., Amboldi, N., Bellotti, V., Arbustini, E., Perfetti, V., Ferrari, M., Zorzoli, I., Marione, M.G., Garini, P. *et al.* (1995), *Proc. Natl. Acad. Sci. USA 92*, 2959-2963; Salomon, A.R., Marcinowski, K.J., Friedland, R.F. and Zagorski, M.G. (1996) *Biochemistry 35*, 13568-13578; Lorenzo, A. and Yankner, B.A. (1994), *Proc. Natl. Acad. Sci. USA 91*, 12243-12247; Tomiyama, T., Shoji, A., Kataoka, K., Suwa, Y., Asano, S., Kaneko, H., Endo, N. (1996), *J. Biol. Chem. 271*, 6839-6844; Howlett, D.R., Perry, A.E., Godfrey, F., Swatton, J.E., Jennings, K.H., Spitzfaden, C., Wadsworth, H., Wood, S.J. and Markwell, R.E. (1999) *Biochem. J. 340*, 283-289; Luo, Y. et al. (2002), *Proc. Natl. Acad. Sci. USA* 99, 12197-12202; J.,E. and Lee, M. (2003) *Biochem. .Biophys. Res. Comm. 303*, 576-579 and the publication by Howlett, D.R., George, A.R., Owen, D.E., Ward, R.V. and Markwell, R.E. (1999) *Biochem. J. 343*, 419-423. These and other relevant results include the three U.S. patents 6,001,331; 5,972,956 and 5,955,472, the patents WO 9628471, WO 9832754-A, JP 090954222, EP 1018511 and the patent SKF-74652.

Other approaches to the treatment of Alzheimer's disease include preventing the formation of pathological amyloid ß-aggregates by using peptides (in this connection, cf. Soto C. (1999), *Rev. Mol. Med. 5*; 343-350).

For the treatment of spinocerebellar ataxia (type 3) the use of small molecules was described by Shirasaki H, Ishida C, Nakajima T, Kamei H, Koide T, Fukuhara N. (2003) [A quantitative evaluation of spinocerebellar degeneration by an acoustic analysis--the effect of taltirelin hydrate on patients with Machado-Joseph disease] Rinsho Shinkeigaku 43, 143-148 and Sakai, T. (1996) [A possibility of therapeutic

trial with tetrahydrobiopterin, which was suggested by the administration of sulfamethoxazole-trimethoprim] Rinsho Shinkeigaku 12, 1324-1325.

Furthermore, additional patents and scientific publications are relevant with respect to the catechins of green tea. For instance, several patents have been granted or applied for which are directed to the ingredients of green tea. The U.S. patent 20020151506 ("Catechins for the treatment of fibrillogenesis in Alzheimer's disease, Parkinson's disease, systemic AA amyloidosis and other amyloid disorders"), U.S. patent 20020086067 ("Catechins and green tea extract for the treatment of amyloidosis in Alzheimer's disease and other amyloidoses") are especially relevant. An examination of the delivery of the catechins of green tea to the brain was described by Yoshida, H. *et al.* (1999) *Biochemical Pharmacology*, 58, 1695-1703. Levites *et al.* described a neuroprotective effect of EGCG on neuroblastoma cells that had been damaged with the Alzheimer peptide amyloid ß-peptide (Levites, Y., Amit, T., Mandel, S. and Youdim, M. B. H. (2003) *FASEB J.* 17, 952-954). The application of the catechins of green tea was not explicitly described and protected for polyglutamine disorders. However, we were able to observe a visible effect in disease models of polyglutamine disorders and would therefore like to seek protection for the application specifically for this group of disorders.

Many of the known compounds are not aimed at a direct interaction with the aggregate-forming proteins but to an indirect interaction, e.g. via heat shock proteins (HSPs). However, it is more useful to influence the formation of aggregates directly since according to current knowledge, they play an essential role in the development of the disease in the case of most disorders. Furthermore, an approach with chemical agents is superior to one with peptides since the latter are generally not delivered to the brain in an efficient manner and, most of the time, also decompose very quickly.

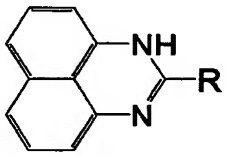
To sum up, it has to be noted that to this date disorders wherein the pathological deposit of proteins is part of the essential disease mechanisms can to a large extent only be treated symptomatically. There is therefore a demand for additional or more effective treatment options for these disorders.

It was therefore the object of the present invention to provide means and methods for the treatment and diagnosis of neurodegenerative disorders and amyloid diseases.

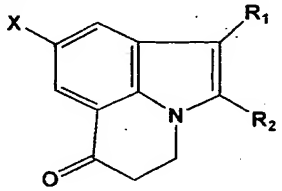
This object is achieved by the provision of the embodiments characterized in the claims.

Consequently, the present invention relates to a pharmaceutical or diagnostic composition comprising one or more active substances wherein the one or more active substance(s) is/are selected from a group consisting of:

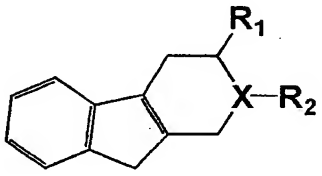
(a) active substances with a structure according to formula I-1 to I-9



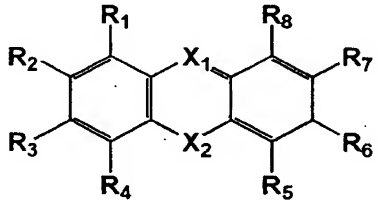
Formula I-1



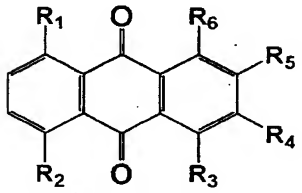
Formula I-2



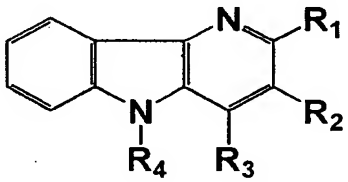
Formula I-3



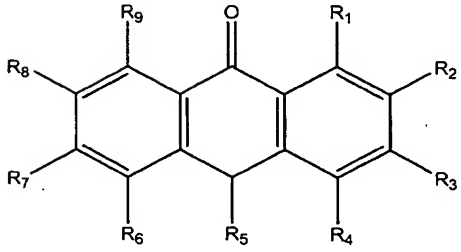
Formula I-4

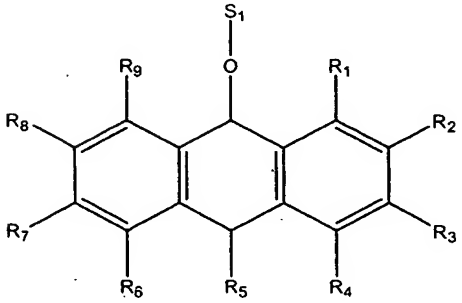


Formula I-5

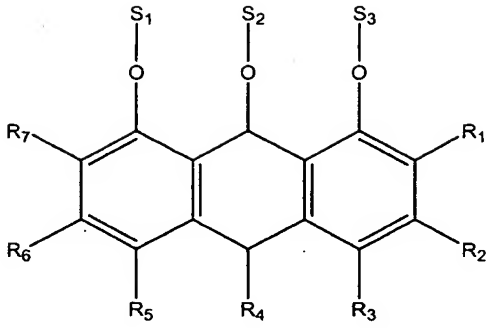


Formula I-6





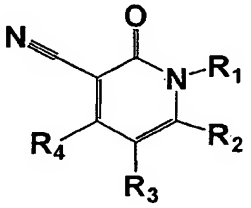
Formula I-7 Formula I-8



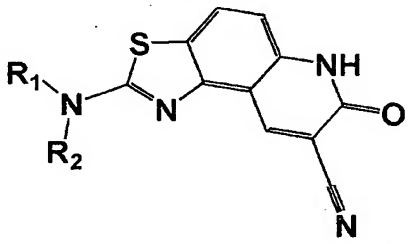
Formula I-9

wherein X in formulas I-2 and I-3 is H, OH, NH_2 or a halogen atom and X_1 and X_2 in formula I-4 are any heteroatom;

(b) active substances with a structure according to formula II-1 or II-2

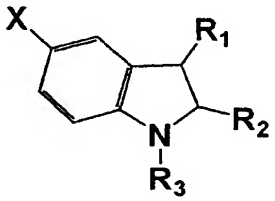


Formula II-1

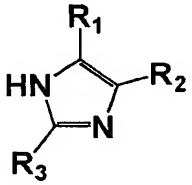


Formula II-2

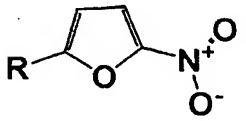
(c) active substances with a structure according to formula III-1 to III-6



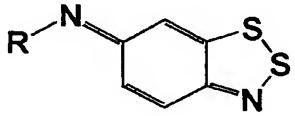
Formula III-1



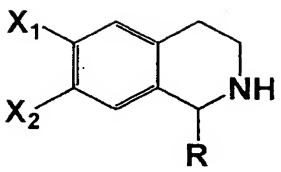
Formula III-2



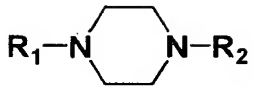
Formula III-3



Formula III-4



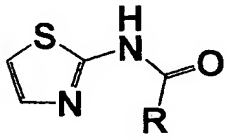
Formula III-5



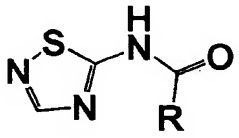
Formula III-6

wherein X in formula III-1 and X_1 and X_2 in formula III-5 are H, OH, NH_2 or a halogen atom;

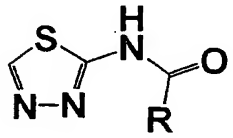
(d) active substances with a structure according to formula IV-1 to IV-6



Formula IV-1

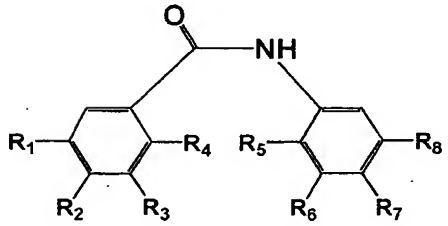


Formula IV-2

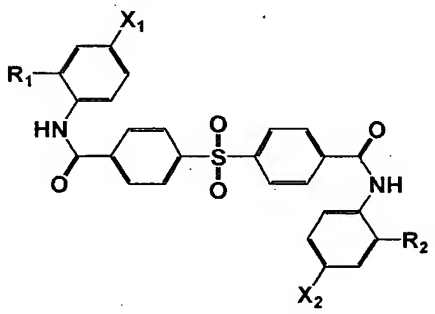


Formula IV-3

Formula IV-4



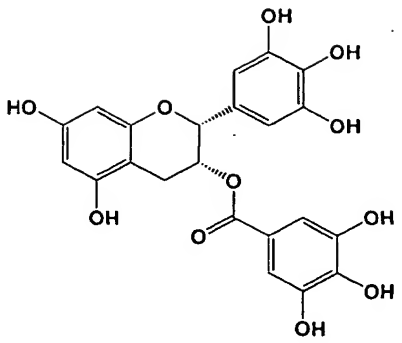
Formula IV-5



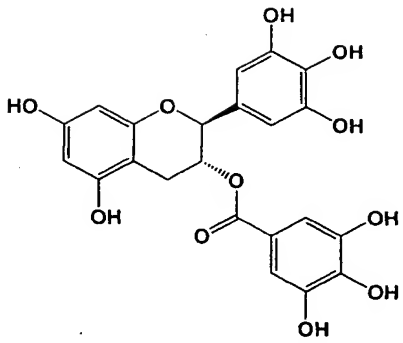
Formula IV-6

X_1 and X_2 in formula IV-6 are selected from H, F, I, Br or Cl, OH or OA, SH or SA, NH_2, NHA_1 or NA_1A_2 or A and wherein A and/or A_1 and A_2 is/are a branched, straight-chain or cyclic alkyl or heteroalkyl group with up to 7 carbon atoms;

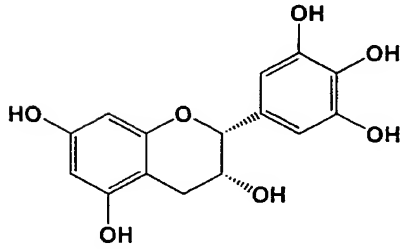
(e) active substances with a structure according to formula V-1 to V-4



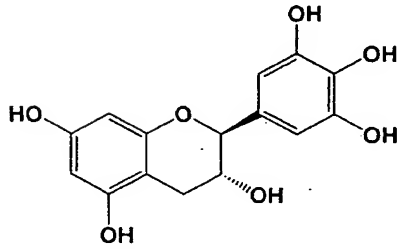
Formula V-1



Formula V-2

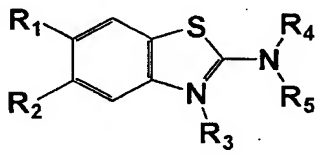


Formula V-3

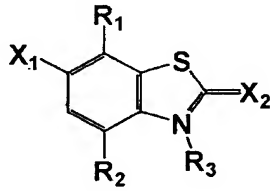


Formula V-4

(f) active substances with a structure according to formula VI-1 or VI-2



Formula VI-1



Formula VI-2

wherein R_1 to R_9 and S_1 to S_3 are selected from

(i) H, OH, NH_2 or a halogen atom;

(ii) single- or multi-branched or straight-chain alkyl or heteroalkyl groups with one or two rings and up to 10 carbon atoms;

(iii) cyclic alkyl or heteroalkyl groups with 1 or 2 rings or aryl or heteroaryl groups with up to 10 carbon atoms each.

The mentioned single- or multi-branched or straight-chain alkyl or heteroalkyl groups comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. The ring or ring systems possible in groups R_1 to R_9 and S_1 to S_3 in turn comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms so that the mentioned groups can comprise a total of up to 20 carbon atoms, whereby any number lower than 20 is specifically envisaged as well. However, it is especially preferred that the number of carbon atoms in groups R_1 to

R_9 and S_1 to S_3 does not exceed a total of 10. Again, any number lower than 10 is specifically envisaged as well.

The person skilled in the art is familiar with the term "heteroatom". In this context, the term particularly refers to, but is not limited to, N, O, Cl, F, Br, I and S. It is preferred that the heteroatoms be present in the form of amides, esters, nitriles and ether compounds.

All the active substances or chemical agents inhibit the aggregation of proteins relevant to a disease which in the case of certain diseases, also known in the prior art as "amyloid diseases", are deposited in the form of amyloids. These diseases include in particular neurodegenerative disorders.

The active substances or chemical agents are suitable for both the diagnosis and the treatment of these disorders. Within the framework of the present invention, the term "active substance" is also used in connection with diagnostic compositions. This is because binding of the active substance to amyloids or aggregates has to occur to allow a positive diagnosis of an amyloid or aggregate formation. This binding is subsumed under the term "effect". In other words, the term "effect" is not restricted to a therapeutic effect.

The conversion of the protein-containing deposits to a form that can be broken down more easily by the organism by means of small molecules or the prevention of the formation of protein aggregates are possibilities of preventing these disorders, slowing their progress or even leading to an improvement and the disappearance of the symptoms. The active substances or chemical agents we identified have the potential of affecting the protein aggregation accordingly. They are not only useful for a therapeutic application or the development thereof but they can also potentially be used for the diagnosis or the evaluation of the progress of diseases based on the pathological deposit of proteins.

The invention offers several advantages compared to known pharmaceutical compositions and methods of treatment:

- An essential characteristic of the pathogenesis mechanism of different neurodegenerative diseases – especially Alzheimer's disease, Parkinson's disease and polyglutamine disorders such as Huntington's chorea – is the insolubilization and the deposit of aggregates of disease-specific proteins: In the case of Alzheimer's disease, it is amyloid-beta, in the case of Parkinson's disease, alpha-synuclein, in the case of polyglutamine disorders, huntingtin or ataxins. The substances presented by us are highly suitable for the treatment of these disorders because they attack at a presumably very early stage of the disease mechanism, namely the deposit of aggregated proteins, and therefore could represent a causal treatment to a much higher degree than previous forms of therapy.
- The chemical agents of the present invention are characterized in that due to their size, structure and distribution coefficient in an octanol/water mixture, they can potentially be delivered to the brain and are therefore suitable for treating disorders of the central nervous system.
- Another advantage is the fact that the substances are relatively easy to synthesize. In the case of catechin derivatives, which are ingredients of green tea, they are even easily accessible natural products.
- The selected substances are stable for an extended period of time.
- A particular advantage lies in the fact that we have been able to prove for a number of these chemical agents that they are not only able to inhibit the aggregation of an individual protein but even the aggregation of different proteins such as huntingtin, ataxin-3 or amyloid-beta. These compounds can therefore potentially be useful in the treatment of not only one but several diseases.
- The substances have already been tested for toxicity in different cell culture models and toxic substances have been eliminated.
- The ingredients of green tea – catechin derivatives – have been proven to be well tolerated and have already been administered to patients in several clinical studies – however, in the course of treatments of cancerous diseases – and the lack of toxic effects has been demonstrated.
- Since there are indications that at least a part of the substances binds directly to protein aggregates (especially of huntingtin and ataxin-3) there is the possibility of using these compounds in diagnostics as well. For this

purpose, the molecules could be labeled – e.g. radioactively – and an accumulation in brain tissue could for example be detected by means of PET (positron emission tomography) technology. This way, a use in diagnostics (especially significant in the case of Alzheimer's disease and Parkinson's disease) and as surrogate markers in the observation of the course of an illness, for example in clinical studies of polyglutamine disorders (Huntington's chorea), would be possible.

The active substances contained in the pharmaceutical and diagnostic compositions according to the present invention can be used as such or after their pharmacological properties have been improved.

Accordingly, the present invention also encompasses pharmaceutical and diagnostic compositions whose above-mentioned active substances have been subjected to an improvement of their pharmacological properties. For this purpose, the molecular scaffold of the active substance is modified further in order to obtain a modified binding site, a modified activity spectrum, a modified organ specificity, an improved activity, a reduced toxicity (an improved therapeutic index), reduced side-effects, a delayed onset of the therapeutic effectiveness or the duration of the therapeutic effectiveness, modified pharmacokinetic parameters (resorption, distribution, metabolism or excretion), modified physicochemical parameters (solubility, hygroscopic properties, color, taste, smell, stability, state of matter), an improved general specificity, organ or tissue specificity, and/or an optimized form and route of administration. This can be achieved by the esterification of carboxy groups, hydroxy groups with carboxylic acids, hydroxy groups to e.g. phosphates, pyrophosphates, sulfates, "hemisuccinates" or the formation of pharmaceutically acceptable salts, pharmaceutically acceptable complexes or the synthesis of pharmacologically active polymers, or the introduction of hydrophilic groups, the introduction and/or the replacement of substituents in aromatics or side chains, the alteration of the substituent pattern or the modification by introducing isosteric or bioisosteric groups, or the synthesis of homologous compounds, and/or the introduction of branched side chains, the conversion of alkyl substituents to cyclic analogues, the derivatization of hydroxy groups to ketals or acetals, the N-acetylation to amides, phenyl carbamates, the synthesis of Mannich bases and/or imines, or the conversion of ketones,

aldehydes in Schiff bases, oximes, acetals, ketals, enol esters, oxazolidines, thiazolidines or combinations thereof.

The different measures described above are generally known. They include or are based on quantitative analyses of structure-activity relationships (QSAR); cf. Kubinyi, "Hausch-Analysis and Related Approaches", Publishing House VCH, Weinheim 1992, as well as combinatory (bio)chemistry, classical chemistry and other approaches; cf. e.g. Holzgrabe and Bechtold, *Deutsche Apotheker Zeitung* 140(8) (2000), 813-823.

In a preferred embodiment of the pharmaceutical or diagnostic composition, the halogen atoms are selected from a group consisting of I, Cl, Br or F.
F is particularly preferred.

In a preferred embodiment of the pharmaceutical or diagnostic composition, the alkyl, heteroalkyl, aryl or heteroaryl groups comprise 1, 2, 3 or 4 heteroatoms each.

In a preferred embodiment of the pharmaceutical or diagnostic composition, the heteroatoms are selected from a group consisting of N, O, or S.

In a preferred embodiment of the pharmaceutical or diagnostic composition, the alkyl, heteroalkyl, aryl or heteroaryl groups comprise 1, 2, 3 or 4 substituents each.

In an especially preferred embodiment of the pharmaceutical or diagnostic composition, the substituents are selected from a group consisting of Cl, F, Br or I.

In a preferred embodiment of the pharmaceutical or diagnostic composition, R_1 and R_2, R_2 and R_3, R_3 and R_4, R_4 and R_5, R_5 and R_6, R_6 and R_7, R_7 and R_8 and/or R_8 and R_9 are bridged via further atoms.

In a preferred embodiment of the diagnostic composition, the active substance or at least one of the active substances is labeled. The labeling is preferably a radioactive labeling.
The binding to aggregates or amyloids as well as the binding site in the organism or a sample taken from the organism can be detected by means of imaging processes,

in the case of radioactive-labeled active substances for example by means of the PET process (positron emission tomography) mentioned above. The process can be carried out in vitro, ex vivo or in vivo.

The possible nuclides are known to the person skilled in the art. They are usually short-lived nuclides with a preferred half-life between 20 minutes and 2 hours which can be prepared in a cyclotron.

The present invention also relates to the use of one or more of the active substances described above for preparing a pharmaceutical or diagnostic composition for the treatment or diagnosis of neurodegenerative disorders or amyloid diseases.

The terms "amyloid" and "amyloid disease" are known to the person skilled in the art. Amyloid is defined by three classical parameters which are used individually or in combination to detect amyloids and thus the presence of amyloid diseases:

- The *Congo red binding* visible in transmitted light under a microscope and the green birefringence visible in polarized light. The latter indication is only pathognomic if the stringent Congo red staining according to Puchtler et. al. is applied.
- The *fibrillar nature* of the deposited proteins, visible under the electron microscope. The fibrils have a thickness of about 10 nm, appear rigid and are partially branched. All amyloid deposits contain fibrils of a similar type. An assay (filter assay, membrane filter test) for detecting the fibrils is described in the European patent application EP 98943817.1 ("Novel method of detecting amyloid-like fibrils or protein aggregates") and herewith explicitly incorporated by reference. In this connection, reference is also made to the membrane filter tests mentioned in the examples (see also Figure 1B), optionally using electron microscopy (Figures 1E and 1F).
- The *beta-sheet structure*. All amyloid fibril proteins examined so far had a beta-sheet structure. Glenner considers this structure to be the pathogenic principle. Beta-sheet fibrils as formed by the amyloid are insoluble in normal buffers and resist enzymatic degradation. They are not recognized as foreign bodies by the organism. Glenner thus appropriately described amyloidoses as beta-fibrilloses.

Selected indications which fall under the definition "amyloid diseases", and how they

are diagnosed for example in clinical medicine, are described in more detail below.

In a preferred embodiment of the pharmaceutical composition, the diagnostic composition or the use, the pharmaceutical or diagnostic composition comprises, in addition to the active substance, one or more pharmaceutically acceptable carriers, diluents or excipients.

Examples of suitable pharmaceutically acceptable carriers and/or diluents are known to the person skilled in the art and include e.g. phosphate-buffered sodium chloride solutions, water, emulsions, such as e.g. oil/water emulsions, different types of wetting agents or detergents, sterile solutions, etc. Pharmaceutical compositions comprising such substrates can be formulated according to known conventional methods. The pharmaceutical compositions can be administered to an individual in a suitable dosage. The administration can be oral or parenteral, e.g. intravenous, intraperitoneal, subcutaneous, intramuscular, local, intranasal, intrabronchial, oral or intradermal, or via a catheter into an artery. Preparations for a parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as e.g. olive oil, and organic ester compounds such as e.g. ethyl oleate which are suitable for injections. Aqueous substrates include water, hydroalcoholic solutions, emulsions, suspensions, salt solutions and buffered media. Parenteral substrates include sodium chloride solutions, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's solution and bonded oils. Intravenous substrates include e.g. liquid, nutritive and electrolyte supplements (such as e.g. those based on Ringer's dextrose). The pharmaceutical composition can also comprise preservatives and other additives, such as e.g. antimicrobial compounds, antioxidants, complex formers and inert gases. Furthermore, depending on the intended specific use, other active substances can be present such as e.g. interleukins, growth factors, differentiation factors, interferons, chemotactic proteins or an unspecific immunomodulator.

The type of dosage is determined by the physician in charge in accordance with the clinical factors. The person skilled in the art is aware of the fact that the type of dosage depends on different factors, such as e.g. the body height and weight, the body surface, the age, sex or general health of the patient, but also on the specific

preparation to be administered, the duration and manner of administration, and on other drugs which may be administered at the same time. A typical dose can e.g. be in a range of between 0.001 and 1,000 μg, wherein doses below and above this exemplary range are also conceivable, in particular when keeping in mind the above-mentioned factors. In general, when administered regularly, the composition according to the present invention should be administered in doses in a range of between 1 μg and 10 mg units per day. In these preparations, the active substances will usually be present in a concentration of more than 10 μg/ml of a physiological buffer. However, they can also be present in solid form at a concentration of 0.1 to 99.5 wt.-% of the total mixture. Generally it has been shown to be advantageous to administer the active substance(s) in total amounts of about 0.001 to 100 mg/kg, preferably in total amounts of about 0.01 to 10 mg/kg body weight, over 24 hours, optionally as a continuous infusion or in the form of several individual doses to achieve the desired result. If the composition is administered intravenously, the dosage should be in the range of between 1 μg and 10 mg units per kilogram body weight per day. The pharmaceutical composition can be administered topically, locally or systemically.

The present invention also relates to methods for the treatment or diagnosis of neurodegenerative disorders or amyloid diseases comprising administering a pharmaceutical compositions according to the present invention or a diagnostic composition according to the present invention to a subject.

In a preferred embodiment of the method, the subject is a human being.

In a preferred embodiment of the use or the method, the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, Parkinson's syndrome and polyglutamine diseases.

Here, it is preferred that Parkinson's syndrome encompass idiopathic Parkinson's disease as well as atypical Parkinson's syndromes associated with protein aggregation; and that polyglutamine diseases encompass Huntington's chorea, spinocerebellar ataxias of types 1, 2, 3, 6, 7 and 17, dentatorubral pallidoluysian atrophy as well as spinobulbar muscular atrophy (Kennedy syndrome).

It is furthermore preferred that the amyloid disease be selected from the group consisting of: Hereditary and non-hereditary prion diseases (kuru, fatal familial insomnia, Gerstmann-Straussler-Scheinker syndrome, Creutzfeld-Jacob disease, new variant of Creutzfeld-Jacob disease), dementia with Lewy bodies, primary systemic amyloidosis, secondary systemic amyloidosis with deposits of serum amyloid A, senile systemic amyloidosis, familial amyloid polyneuropathy types I and III, familial nonneuropathic amyloidosis, familial British dementia, hereditary cerebral amyloid angiopathy, hemodialysis-associated amyloidosis, familial amyloidosis-Finnish type, diabetes mellitus type II, hereditary renal amyloidosis, injection amyloidosis with deposits of insulin, medullary carcinoma of the thyroid with deposits of calcitonin, atrial amyloidosis with deposits of ANF, inclusion body myositis.

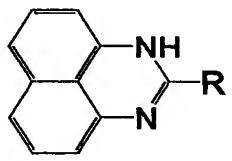
As has already been explained in the description of the main embodiment, the active substances or chemical agents contained in the pharmaceutical or diagnostic compositions according to the present invention can be divided into 6 groups based on their chemical structure. In the following, these groups will be described in detail.

Group I

This group contains polycyclic compounds whose outstanding characteristic is the presence of at least tricyclic aromatic groups. The aromatic functional groups are either bonded to numerous hydroxy groups or contain oxo groups, or substitutions with oxygen or nitrogen atoms occur in the aromatic rings themselves.

In particular, this includes the derivatives of the following molecular scaffolds:

Molecular scaffold I-1:

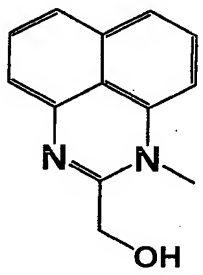


R can be:

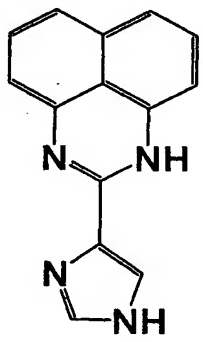
- H, OH, NH_2, Hal

- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

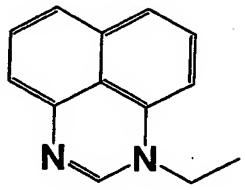
Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with a structure according to formula I-1, wherein the active substance is selected from:



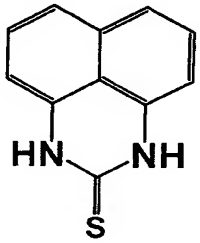
(1-Methyl-1*H*-perimidine-2-yl)-methanol



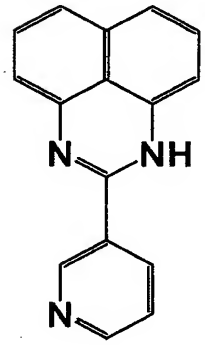
2-(1H-Imidazole-4-yl)-1H-perimidine



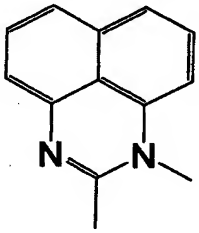
1-Ethyl-1*H*-perimidine



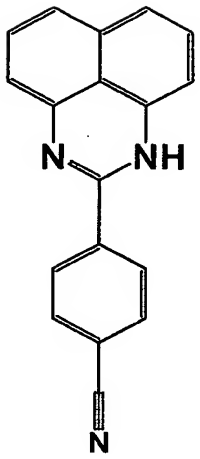
1*H*,3*H*-Perimidine-2-thione



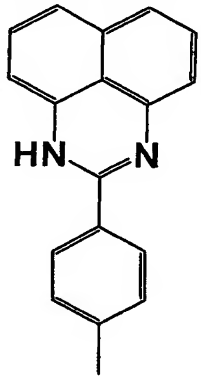
2-Pyridine-3-yl-1H-perimidine



1,2-Dimethyl-1*H*-perimidine

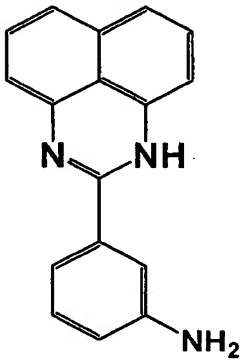


4-(1H-Perimidine-2-yl)-benzonitrile

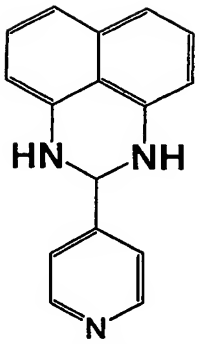


2-*p*-Tolyl-1*H*-perimidine

5



3-(1H-Perimidine-2-yl)-phenylamine

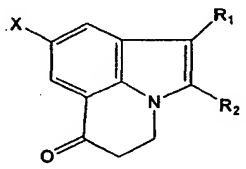


2-Pyridin-4-yl-2,3-dihydro-1*H*-perimidine

Other pharmaceutical or diagnostic compositions according to the present invention comprise active substances selected from the following derivatives:

2-(1H-Imidazole-4-yl)-1H-perimidine and
2-pyridine-3-yl-1H-perimidine

Molecular scaffold I-2:



4,5-Dihydro-pyrrolo[3,2,1-ij]quinoline-6-one

X can be:

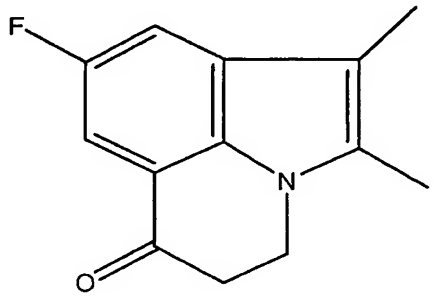
- H, OH, NH_2, Hal

R_1 to R_2 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above

- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

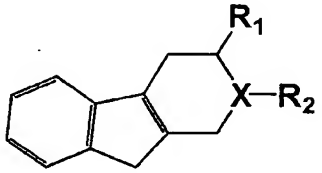
Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with a structure according to formula I-2, wherein the active substance is



8-fluoro-1,2-dimethyl-4,5-dihydro-pyrrolo[3,2,1-ij]quinoline-6-one.

Molecular scaffold I-3:

Tetrahydrofluorene



X can be any heteroatom, specifically, N, O, P and S are possible atoms

R_1 to R_2 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds

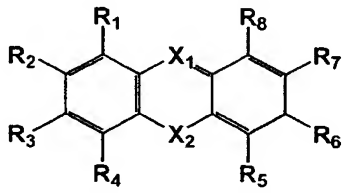
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 to R_2 can be bridged independently or via further atoms

The following compound shall be mentioned as an example of this subgroup:

2-Furan-2-yl-2,3,4,9-tetrahydro-1H-indenol[2,3-c] pyridine-3-carboxylic acid methyl ester

Molecular scaffold I-4:

Anthracene

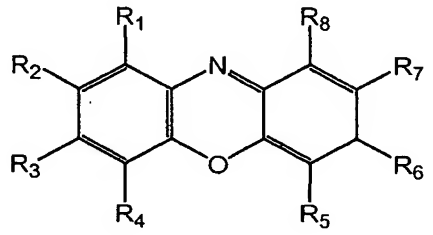


X_1 and X_2 can be any heteroatom, however, in particular N, O, P and S

R_1 to R_8 can be:

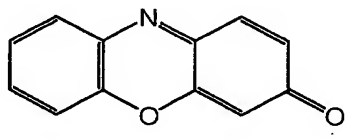
- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2, R_2 and R_3, R_3 and R_4, R_5 and R_6, R_6 and R_7, and R_7 and R_8 can be bridged independently or via further atoms

Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with a structure according to formula I-4, wherein the active substance is:

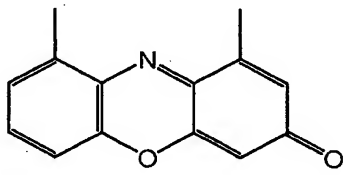


3H-Phenoxazine

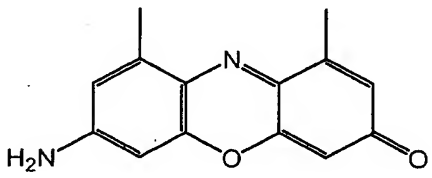
Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with the above structure, wherein the active substance is selected from:



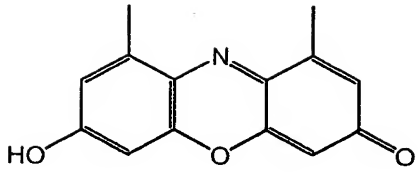
Phenoxazine-3-one



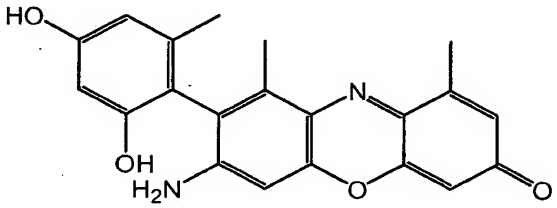
1,9-dimethyl-phenoxazine-3-one



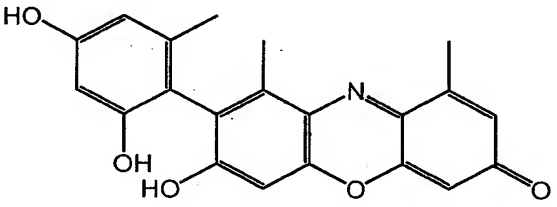
7-amino-1,9-dimethyl-phenoxazine-3-one



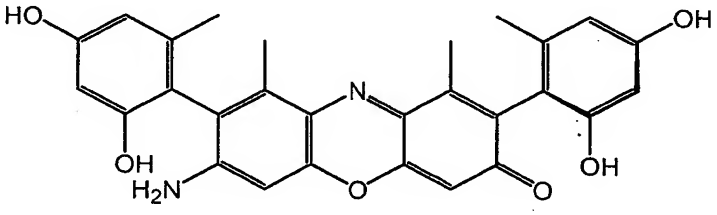
7-hydroxy-1,9-dimethyl-phenoxazine-3-one



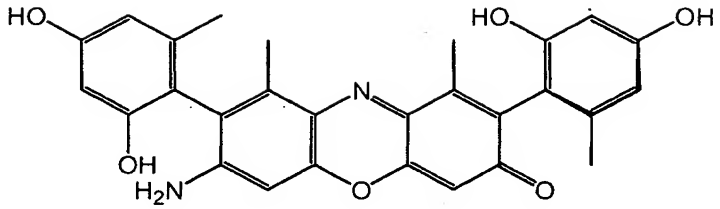
7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one (alpha-amino-orcein)



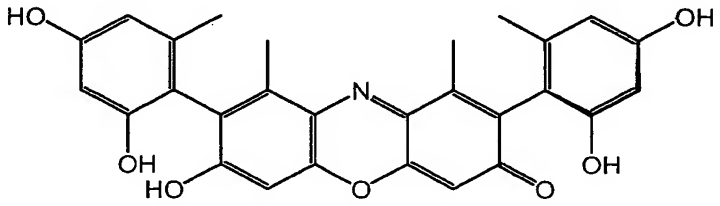
8-(2,4-dihydroxy-6-methyl-phenyl)-7-hydroxy-1,9-dimethyl-phenoxazine-3-one (alpha-hydroxy-orcein)



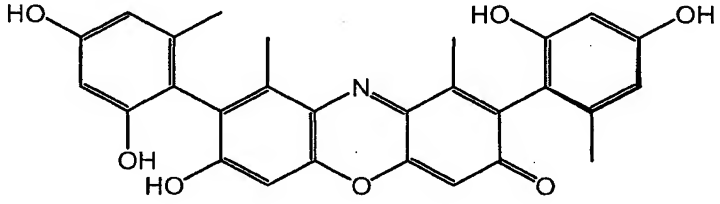
7-amino-2,8-bis-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one (beta-amino-orcein)



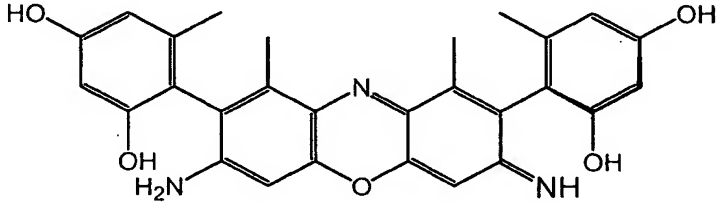
7-amino-2,8-bis-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one (gamma-amino-orcein)



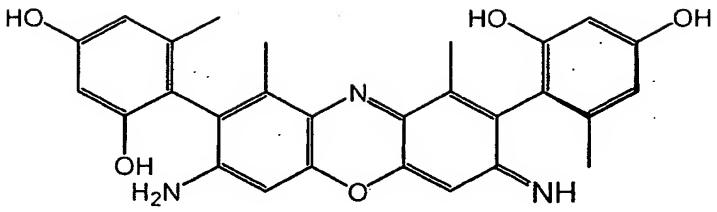
2,8-bis-(2,4-dihydroxy-6-methyl-phenyl)- 7-hydroxy-1,9-dimethyl-phenoxazine-3-one (beta-hydroxy-orcein)



2,8-bis-(2,4-dihydroxy-6-methyl-phenyl)- 7-hydroxy-1,9-dimethyl-phenoxazine-3-one (gamma-hydroxy-orcein)



beta-amino-orceimine



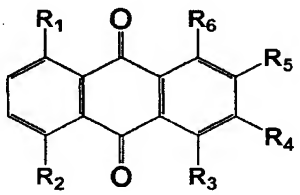
gamma-amino-orceimine

Other pharmaceutical or diagnostic compositions according to the present invention comprise active substances selected from the following derivatives:

7-Amino-8-[2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one

7-amino-1,8,10a,11-tetraydroxy-10,12-dioxo-6,6a,7,10,10a,12-hexahydro-5aH-5-thia-naphthacene-9-carboxylic acid amide

Molecular scaffold I-5:

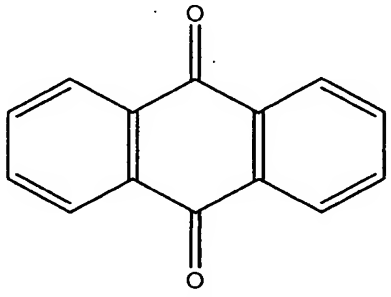


4a, 9a-Dihydro-anthraquinone

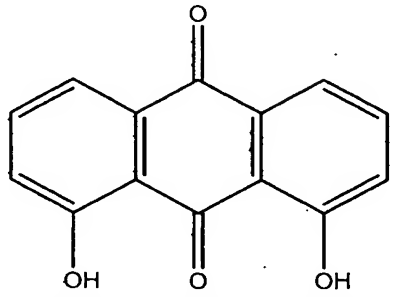
R_1 to R_6 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_3 and R_4, R_4 and R_5, and R_5 and R_6 can be bridged independently or via further atoms

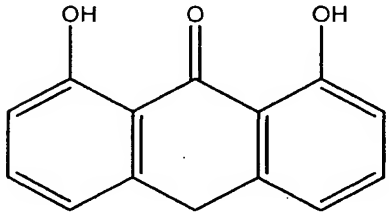
Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with a structure according to formula I-5 or formula I-7 described above, wherein the active substance is:



Anthraquinone

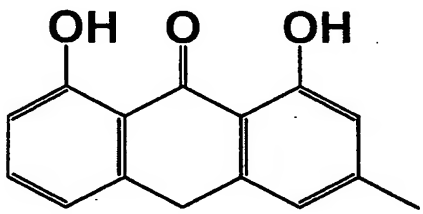


1,8-Dihydroxy-anthraquinone (Danthron)



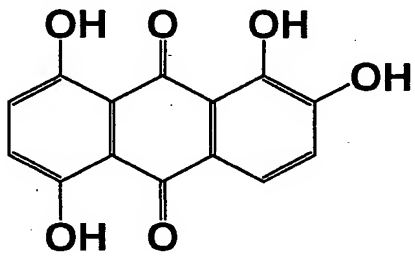
1,8-Dihydroxy-10H-anthracene-9-one

(Dithranol/ Anthralin)

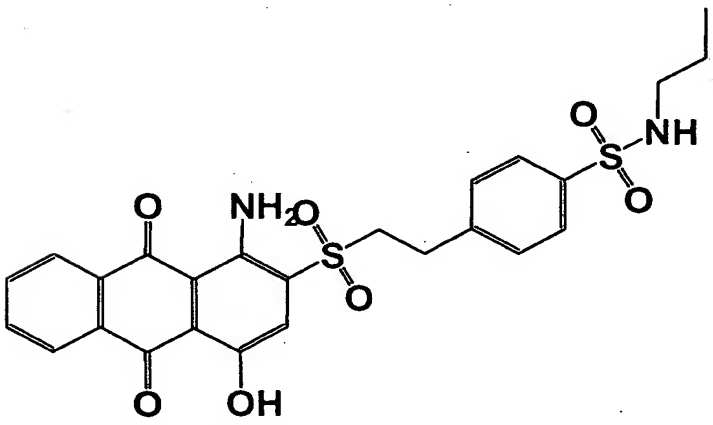


1,8-Dihydroxy-3-methyl-10H-anthracene-9-one

(Chrysarobin)

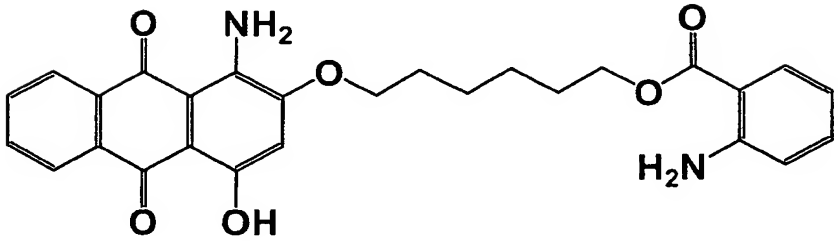


1,2,5,8-Tetrahydroxy-anthraquinone



4-[2-(1-Amino-4-hydroxy-9,10-dioxo-9,10-dihydro-anthracene-2-sulfonyl)-

ethyl]-N-propyl-benzenesulfonamide

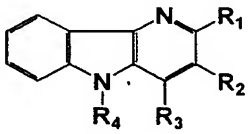


2-Amino-benzoic acid-6-(1-amino-4-hydroxy-9,10-dioxo-9,10-dihydro-anthracene-2-yloxy)-hexyl-ester

Other pharmaceutical or diagnostic compositions according to the present invention comprise active substances selected from the following derivatives:

4-[2-(1-Amino-4-hydroxy-9,10dioxo-9,10-dihydro-anthracene-2-sulfonyl)-ethyl]-N-propyl-benzenesulfonamide,
2-amino-benzoic acid 6-(1-amino-4-hydroxy-9,10-dioxo-9,10-dihydro-anthracene-2-yloxy)-hexylester,
1,8-dihydroxy-3-methyl-10H-anthracene-9-one and
1,2,5,8-tetrahydroxy-anthraquinone.

Molecular scaffold I-6:



10H-Indolo[3,2b-]quinoline

R_1 to R_4 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds

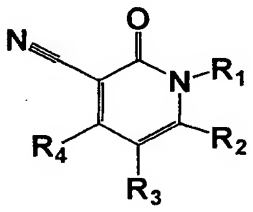
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2, R_2 and R_3, and R_3 and R_4 can be bridged independently or via further atoms

An example of this group is
10-Benzyl-10H-indolo[3,2-b]quinoline-11-carboxylic acid benzyl ester

Group II

The chemical agents of group II comprise a 2-oxo-1,2-dihydro-pyridine-3-carbonitrile group (molecular scaffold II-1). Most substances are characterized by a special modification of this structure. This compound (2-amino-7-oxo-6,7-dihydro-thiazole[4,5-f]quinoline-8-carbonitrile) is referred to as molecular scaffold II-1 in Table 1. Table 1 lists all the structures of group II including their structure, chemical name, molecular weight and empirical formula.

Molecular scaffold II-1



Basic structure: 2-Oxo-1,2-dihydro-pyridine-3-carbonitrile

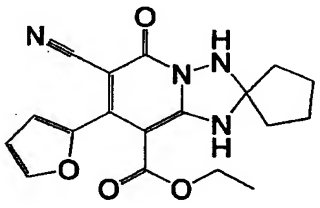
The invention encompasses derivatives of the molecular scaffold II-1,

R_1, R_2, R_3 and R_4 can be:

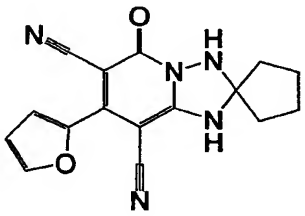
- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each

- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

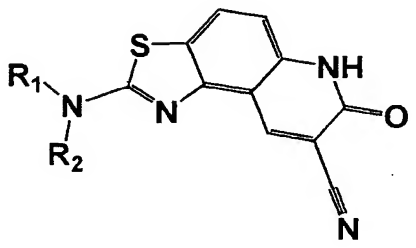
As an example, in particular the compounds represented by the structural formulas below should be protected:



and



Molecular scaffold II-2



Basic structure: 2-Amino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile

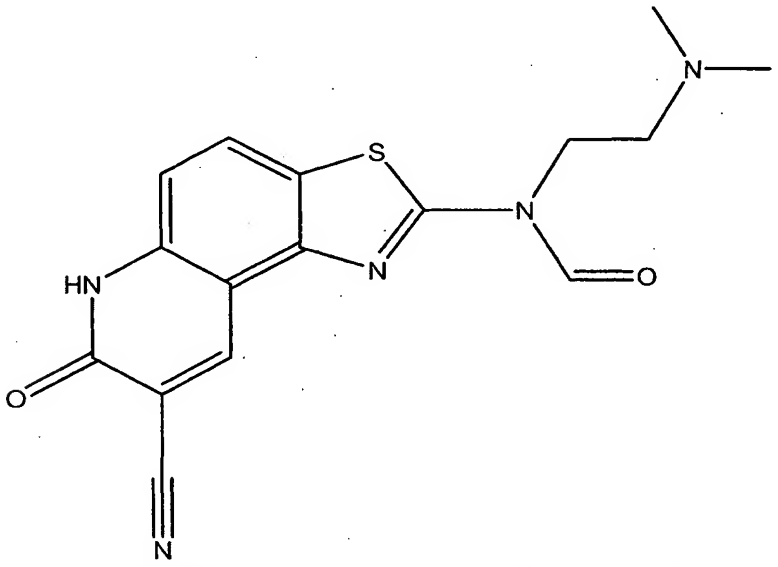
The invention encompasses derivatives of the molecular scaffold II-2,

wherein R_1 and R_2

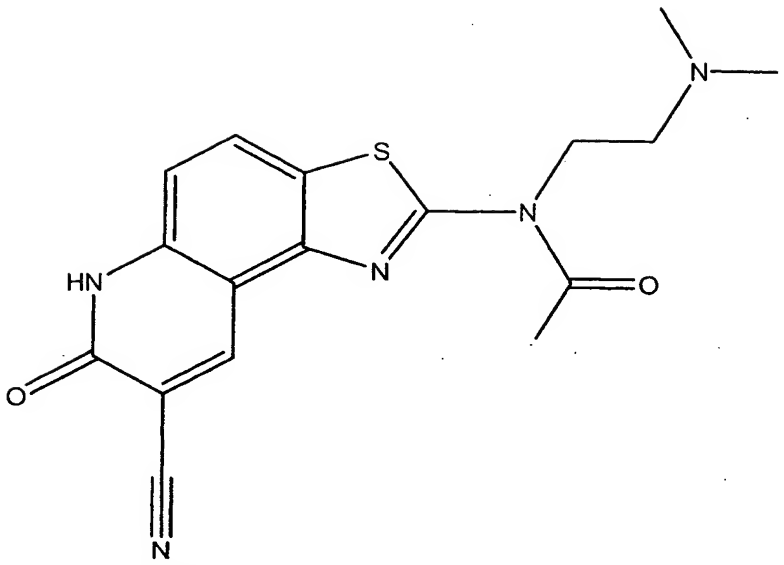
- H, OH, NH_2, Hal

- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

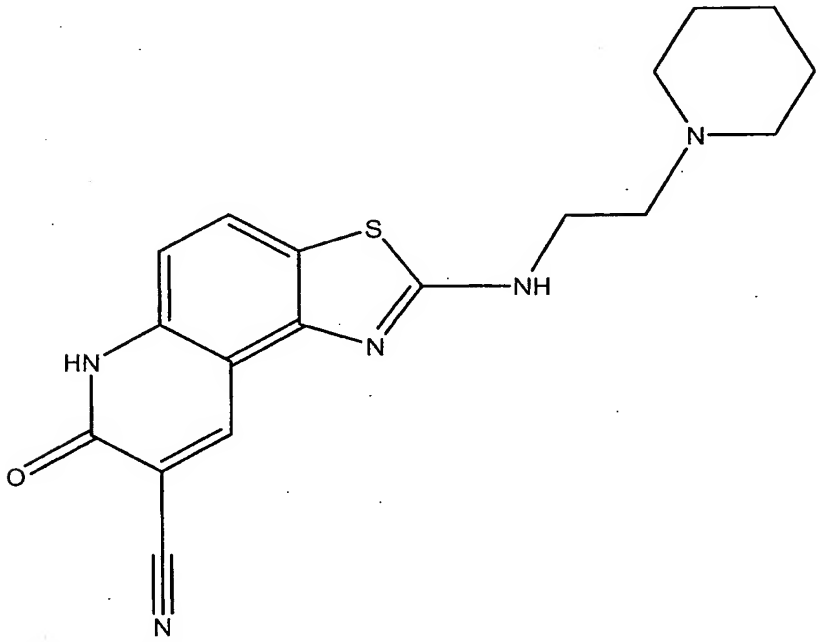
Preferred pharmaceutical or diagnostic compositions according to the present invention comprise an active substance with a structure according to formula II-2, wherein the active substance is selected from:



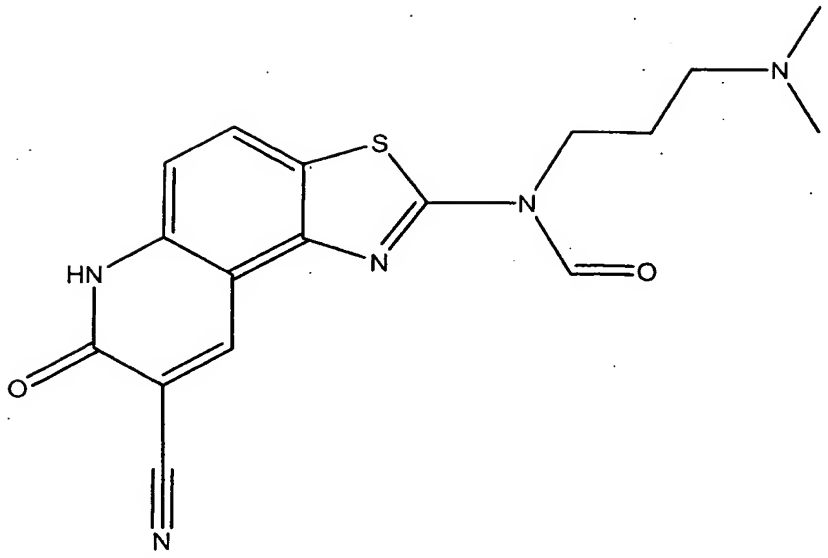
N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinolin-2-yl)-*N*-(2-dimethylamino-ethyl)-formamide



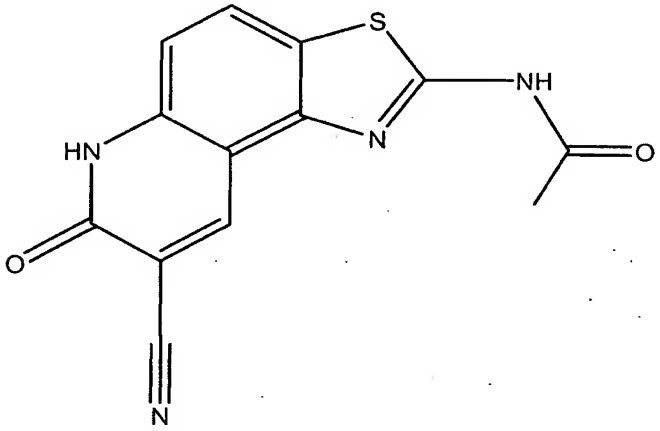
N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinolin-2-yl)-*N*-(2-dimethylamino-ethyl)-acetamide



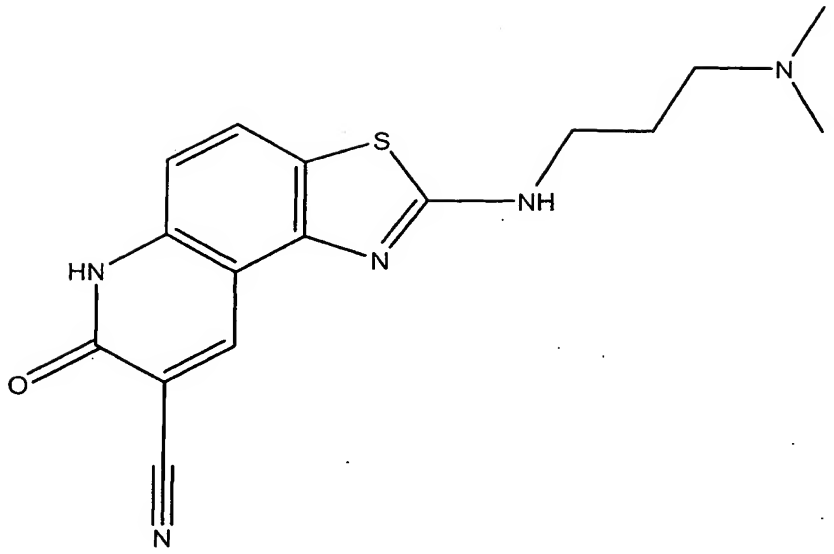
7-Oxo-2-(2-piperidin-1-yl-ethylamino)-6,7-dihydro-thiazolo[4,5-*f*]quinoline-8-carbonitrile



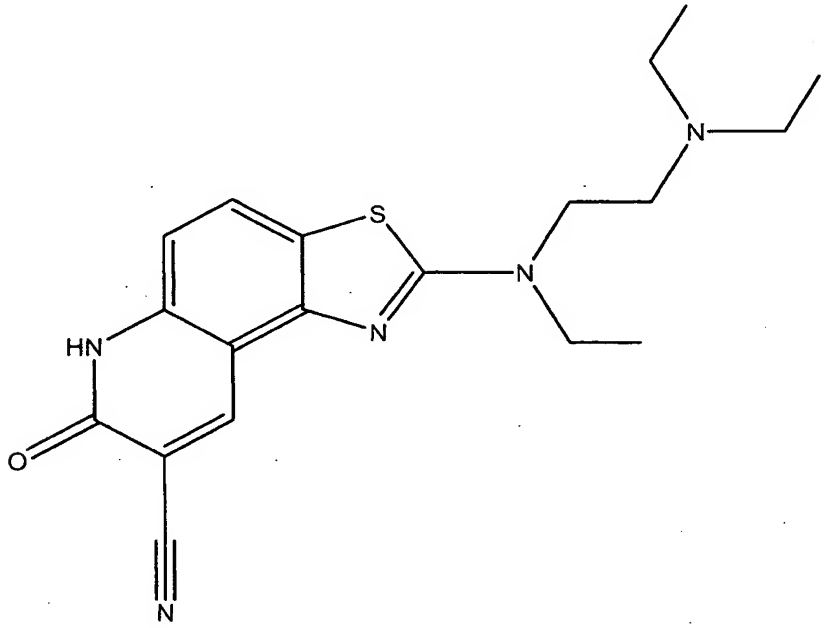
N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinolin-2-yl)-*N*-(3-dimethylamino-propyl)-formamide



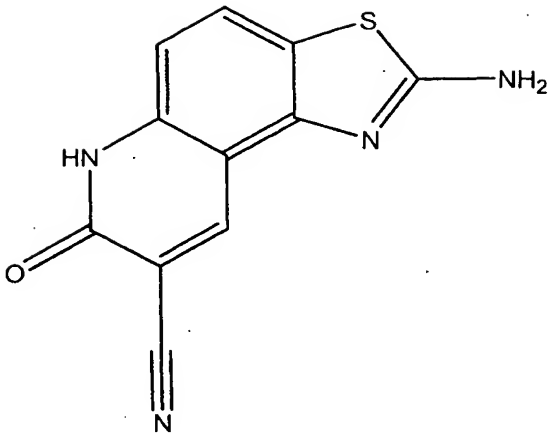
N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinolin-2-yl)-acetamide



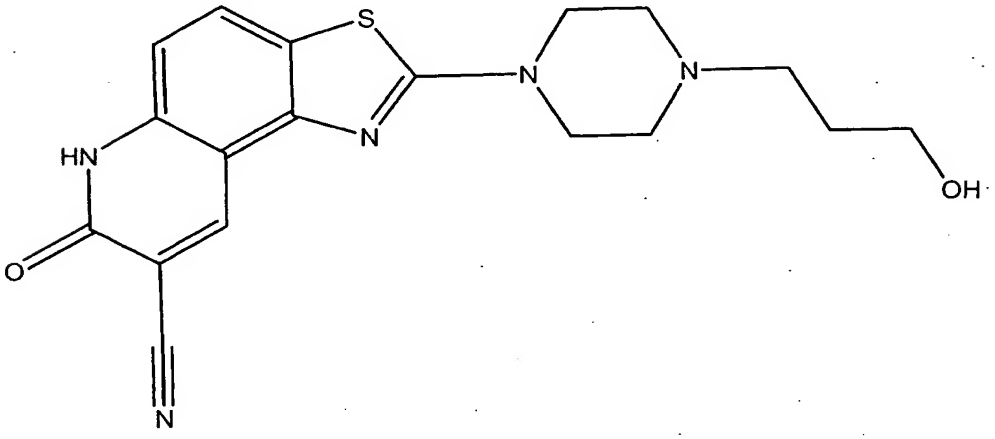
2-(3-Dimethylamino-propylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinoline-8-carbonitrile



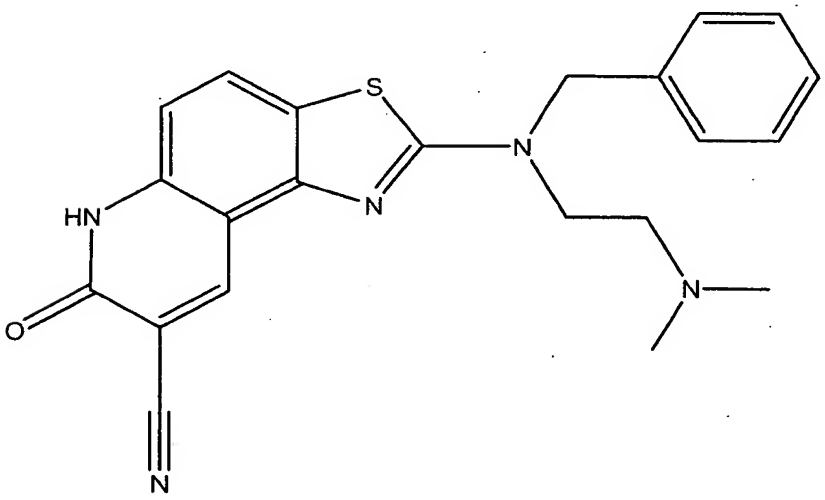
2-[(2-Diethylamino-ethyl)-ethyl-amino]-7-oxo-6,7-dihydro-thiazolo[4,5-*f*]quinoline-8-carbonitrile



2-Amino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile



2-[4-(3-Hydroxy-propyl)-piperazine-1-yl]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile



2-[Benzyl-(2-dimethylamino-ethyl)-amino]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile

Other pharmaceutical or diagnostic compositions according to the present invention comprise active substances selected from the following derivatives:

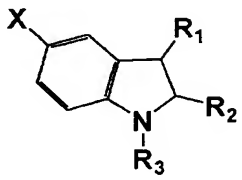
1. N-Benzyl-N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile
2. 2-(2-Hydroxy-ethylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile
3. N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline2-yl)-N-(3-dimethylamino-propyl)-formamide
4. 2-[Benzyl-(2-dimethylamino-ethyl)-amino]7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile
5. N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline2-yl)-N-(2-dimethylamino-ethyl-formamide
6. 7-Oxo-2-(2-piperidine-1-yl-ethylamino)-6,7-dihydrothiazolo[4,5-f] quinoline-8-carbonitrile
7. N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline2-yl)-N-(2-dimethylamino-ethyl)-acetamide
8. 2-[4-(3-Hydroxy-propyl)-piperazine-1-yl]-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
9. 2-Ethylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
10. 2-Dimethylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
11. 2-Diisopropylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
12. (4-Methoxy-phenylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile
13. N-(-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-2-yl)-acetamide
14. 2-Benzylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
15. 2-(4-Methoxy-benzylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f] quinoline-8-carbonitrile
16. N-(8-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-N-(3-dimethylamino-propyl)-acetamide
17. 7-Oxo-2-(2-pyridine-2-yl-ethylamino)-6,7-dihydrothiazolo[4,5-f] quinoline-8-carbonitrile

Group III

Compounds of group III are characterized by the presence of a nitrogen- or oxygen-containing heterocycle. Group III includes 6 molecular scaffolds (molecular scaffolds III-1 to III-6) (Table 3).

Molecular scaffold III-1:

1H-Indole



X can represent: H, OH, NH_2, Hal

R_1 to R_3 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 as well as R_2 and R_3 can be bridged independently or via further atoms

Molecular scaffold III-2:

1H-Imidazole

R_1 to R_3 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

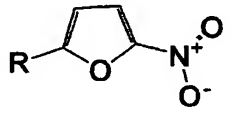
Examples of the substance group:

3-(4-Nitro-imidazole-1-yl)-phenylamine

2-chloro-1H-benzoimidazole-5,6-diamine

5-(2,4-dihydroxy-benzylidene)-2-thioxo-imidazolidine-4-one

Molecular scaffold III-3:



2-Nitro-furan

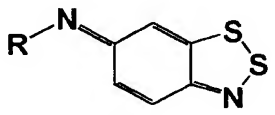
R can be:

- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds

- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

Examples of the substance group:
[3-(5-Nitro-furan-2-yl)-allylidene]-thiazole-2-yl-amine
[3,(5-nitro-furan-2-yl)-allylidene]-pyridine-2-yl-amine

Molecular scaffold III-4:



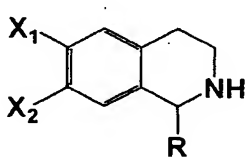
Benzo[1,2,3]dithiazole-6-ylideneamine

R can be:

- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

Examples of the substance group:
N-Benzo[1,2,3]dithiazole-6-ylidene-benzene-1,4-diamine

Molecular scaffold III-5:



1,2,3,4-Tetrahydro-isoquinoline

X_1 and X_2 can represent:

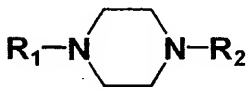
- H, OH, NH_2, Hal

R can be:

- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

Examples of this substance group:
1-(3,4-Dihydroxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline-6,7-diol

Molecular scaffold III-6:



Piperazine

R_1 and R_2 can represent:

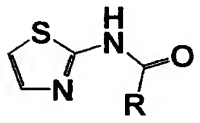
- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each

- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains or aryl groups which can comprise heteroatoms as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

Examples of this substance group:
2,4-Bis-[4-(4-methyl-thiazole-2-yl)-piperazine-1-yl]-pyrimidine
thiophene-2-yl-acetylic acid4-(4-acetyl-piperazine-1-yl)-phenyl-ester

Group IV

The compounds of this group comprise acid amides which are bonded covalently to cyclic aromatic compounds. Group IV consists of a total of 6 molecular scaffolds (Table 4).

Molecular scaffold IV-1: 

N-Thiazole-2-yl-formamide

R can be:

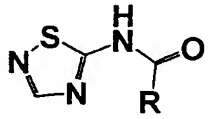
- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds

- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

Example of this substance group:

5-[4-(Thiazole-2-yl-carbamoyl)-phenyl]-furan-2-carboxylic acid-thiazole-2-ylamide

Molecular scaffold IV-2:



N-[1,2,4]Thiadiazole-5-yl-formamide

R can be:

- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

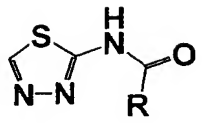
Examples of this substance group:

5-[3-(3-Phenyl-[1,2,4]thiadiazole-5-yl)-ureido]-isophthalic acid dimethyl ester

4-methyl-2-[3-(3-phenyl-[1,2,4]thiadiazole-5-yl)-ureido]-pentanoic acid ethyl ester

carbazole-9-carboxylic acid(e-phenyl-[1,2,4]thiadiazole-5-yl)-amide

Molecular scaffold IV-3:



N-[1,3,4]Thiadiazole-2-yl-formamide

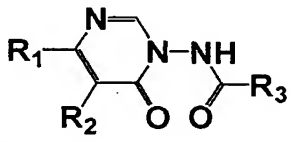
R can be:

- H, OH, NH_2, Hal
- a single- or multi-branched or straight-chain alkyl chain which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- a cyclic alkyl chain with 1 or 2 rings or an aryl compound with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

Example of this substance group:

9,10,10-Trioxo-9,10-dihydro-10l6-thioxanthene-3-carboxylic acid-[1,3,4]thiadiazole-2-ylamide

Molecular scaffold IV-4:



N-(6-Oxo-6H-pyrimidine-1-yl)-formamide

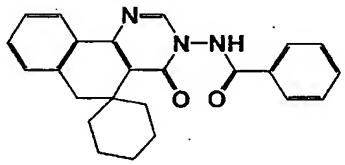
R_1 to R_3 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each

- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2 can be bridged independently or via further atoms

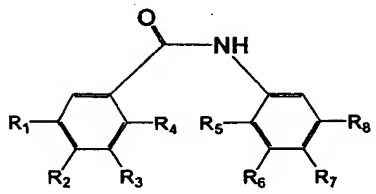
Examples of this substance group:

Since no unambiguous designation of this substance could be found, the structural formula is given to identify this substance:



Molecular scaffold IV-5:

n-Phenyl-benzamide



R_1 to R_8 can be:

- H, H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles or ether compounds

- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

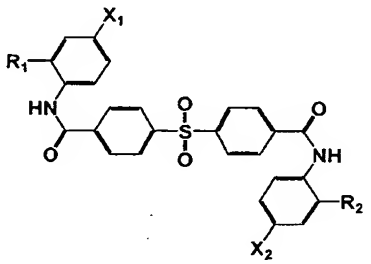
Examples include:

N-[3-(3-{3-[(2-Carboxy-phenyl-1-enecarbonyl)-amino]-phenyl}-acryloyl)-phenyl]-phthlalic acid,

acetic acid 2,6-diacetoxy-4-(4-phenoxy-phenylcarbamoyl)-phenyl ester and

5-(4-chloro-benzoylamino)-2,4-dihydroxy-isophthalic acid dimethyl ester

Molecular scaffold IV-6:



X_1 and X_2 can be:

- H, F, I, Br or Cl, OH or OA, SH or SA, NH_2, NHA_1 or NA_1A_2 or A
- A and/or A_1 and A_2 can be a branched, straight-chain or cyclic alkyl group with 1, 2, 3, 4, 5 or 6 carbon atoms, an aromatic group with 3, 4, 5, 6 or 7 carbon atoms or combinations thereof, wherein individual carbon atoms can also be replaced with 1, 2, 3 or 4 S, N or O atoms.

R_1 and R_2 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each

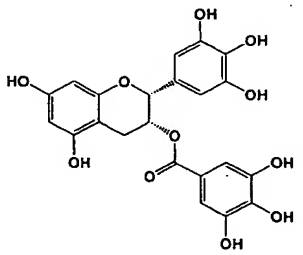
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles, acetals, ketals or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

As examples, the following compounds should explicitly be protected:
2-{4-[4-(2-Cyano-phenylcarbamoyl)-benzenesulfonyl]-benzoylamino}-3-cyano-benzene and
2-{4-[4-(2-carboxy-4-hydroxy-phenylcarbamoyl)-benzenesulfonyl]-benzoylamino}-5-hydroxy-benzoic acid

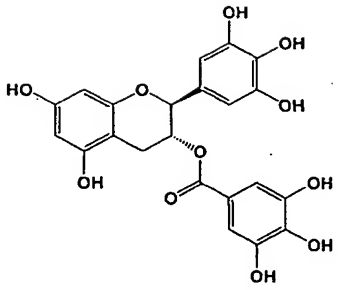
Group V

Group V contains 4 catechins, which are ingredients of green tea. For this group, patent protection is only sought for the use of the substances and their derivatives in the diagnosis and treatment of Huntington's chorea and other diseases wherein a pathological deposit of polyglutamine-containing proteins is observed. All the structures of group V are listed in the annex, Table 5, including their structure, chemical name, molecular weight and empirical formula. They are the following structures and their derivatives:

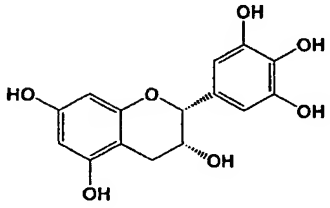
(-)-Epigallocatechin gallate (EGCG) (Formula V-1)



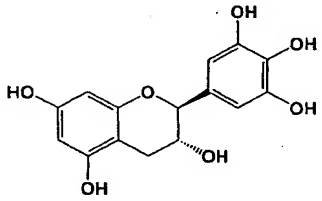
(-)-Gallocatechin gallate (GCG) (Formula V-2)



(-)-Epigallocatechin (EGC) (Formula V-3)



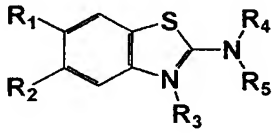
(-)-Gallocatechin (GC) (Formula V-4)



Group VI

The chemical agents of this group comprise benzothiazole compounds. Group VI encompasses two molecular scaffolds VI-1 and VI-2 (Table 6).

Molecular scaffold VI-1:



2-Aminobenzothiazole

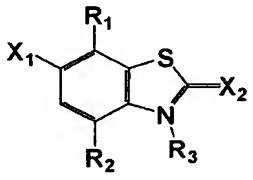
R_1 to R_5 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each

- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles, acetals, ketals or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F
- R_1 and R_2, R_3 and R_5, and R_4 and R_5 can be bridged independently or via further atoms

Protection is sought explicitly for the following derivatives of molecular scaffold VI-1:
N-(6-Amino-benzothiazole2-yl)-acetamide
(4-benzothiazole-2-yl-[1,4]diazepan-1-yl)-furan-2-yl-methanone
2-isopropylamino-6H-thiazolo[4,5-f]quinoline-7-one and
(1,3-dimethyl-1,3-dihydro-benzoimidazole-2-ylidenemethyl)-3,6-dimethyl-2,3-dihydro-benzothiazole-2-yl)-diazene

Molecular scaffold VI-2:



Benzothiazole

X_1 can be:

- H, F, I, Br or Cl, OH or OA, SH or SA, NH_2, NHA_1 or NA_1A_2 or A
- A and/or A_1 and A_2 can be a branched, straight-chain or cyclic alkyl group with 1, 2, 3, 4, 5 or 6 carbon atoms, an aromatic group with 1, 2, 3, 4, 5, 6 or 7 carbon atoms or combinations thereof, wherein individual carbon atoms can also be replaced with 1, 2, 3 or 4 S, N or O atoms.

X_2 can be: O or S

R_1 to R_3 can be:

- H, OH, NH_2, Hal
- single- or multi-branched or straight-chain alkyl chains which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- cyclic alkyl chains with 1 or 2 rings or aryl compounds with 1 or 2 rings which can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms each
- the mentioned alkyl or aryl groups can also each comprise 1, 2, 3 or 4 heteroatoms such as N, O, Cl, F, Br, I or S, in particular also in the form of amides, esters, nitriles, acetals, ketals or ether compounds
- the cyclic compounds can be connected to the basic structure via alkyl chains which can comprise heteroatoms such as N, O, Cl, F, Br, I or S as described above
- Hal can represent: I, Cl, Br or F

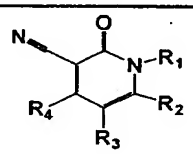
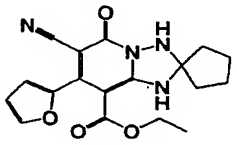
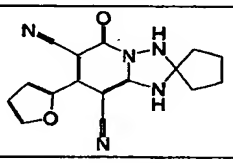
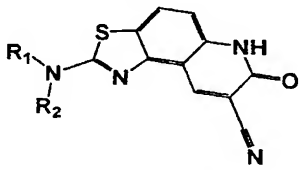
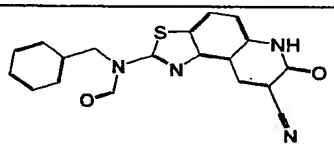
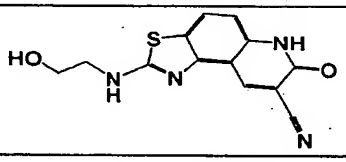
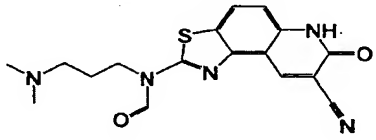
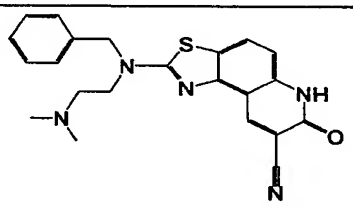
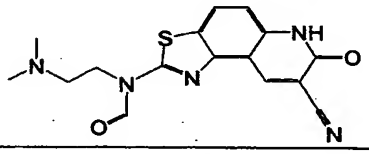
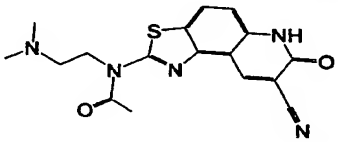
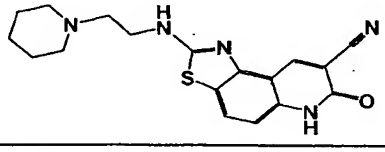
- R_2 and R_3 can be bridged independently or via further atoms

Example of derivatives of molecular scaffold VI-2:
6-Methoxy-3,4,7-trimethyl-3H-benzothiazole-2-one

Derivatives

The present invention also relates to pharmaceutical or diagnostic compositions comprising derivatives of one or more of the active substances mentioned above. Derivatives particularly include those that can for example be obtained by modifications such as the esterification of hydroxy groups with organic and inorganic acids, the introduction or replacement of substituents in aromatics or side chains, the derivatization of hydroxy groups to acetals or ketals, the N-acetylation to amides or phenyl carbamates, the introduction of isosteric or bioisosteric units, the synthesis of Mannich bases or imines, the introduction of branched side chains, the transformation of ketones or aldehydes into Schiff bases, oximes, acetals, ketals, enol esters, oxazolidines, thiazolidines, the replacement of simple side chains with branched side chains and vice versa, the conversion of alkyl substituents to cyclic analogues, or by combinations of these modifications.

Table 1: Group II

EMD	No	Structure	Chemical name	Molecular weight	Empirical formula
45060	Molecular scaffold II-1		Basic structure: 2-Oxo-1,2-dihydro-pyridine-3-carbonitrile	120,1	C6H4N2O
220677	# 1		?	354,4	C18H18N4O4
208067	# 2		?	307,3	C16H13N5O2
	Molecular scaffold II-2		Basic structure: 2-Amino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	242,3	C13H6N4O2S
46618	# 3		N-Benzyl-N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	360,4	C19h12N4O2S
46119	# 4		2-(2-Hydroxy-ethylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	286,3	C13H10N4O2S
46624	# 5		N-(8-Cyano-7-oxo-6,7-dihydro thiazolo[4,5-f]quinoline2-yl)-N-(3-dimethylamino-propyl)-formamide	355,4	C17H17N5O2S
47659	# 6		2-[Benzyl-(2-dimethylamino-ethyl)-amino]7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	403,5	C22H21N5OS
46801	# 7		N-(8-Cyano-7-oxo-6,7-dihydro thiazolo[4,5-f]quinoline2-yl)-N-(2-dimethylamino-ethyl-formamide	341,4	C16H15N5O2S
46802	# 8		7-Oxo-2-(2-piperidine-1-yl-ethylamino)-6,7-dihydrothiazolo[4,5-f]quinoline-8-carbonitrile	353,4	C18H19N5OS
46832	# 9		N-(8-Cyano-7-oxo-6,7-dihydro thiazolo[4,5-f]quinoline2-yl)-N-(2-dimethylamino-ethyl)-acetamide	355,4	C17H17N5O2S

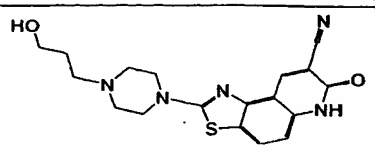
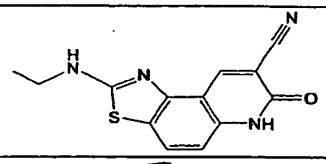
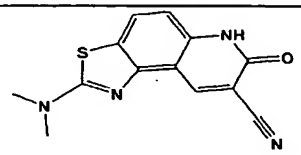
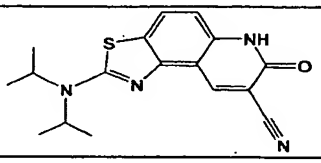
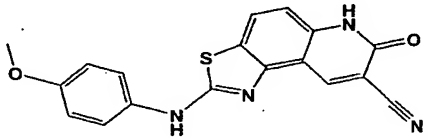
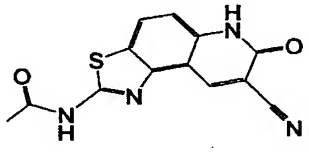
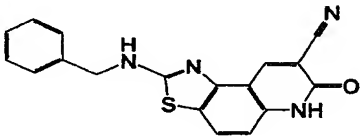
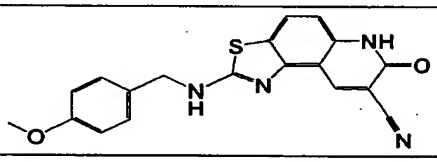
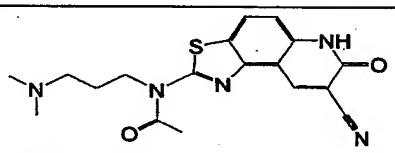
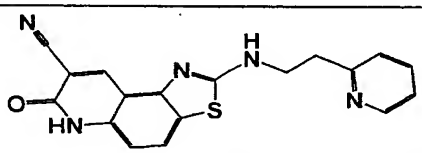
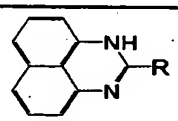
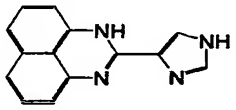
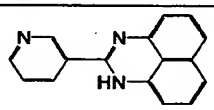
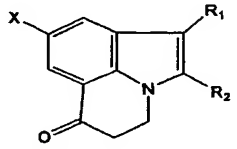
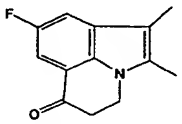
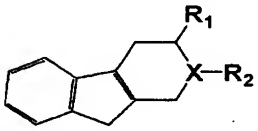
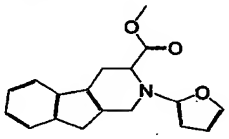
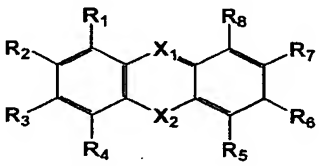
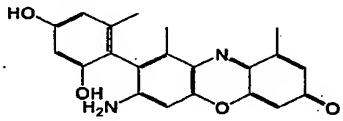
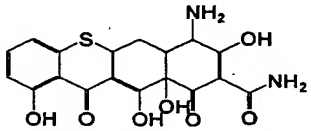
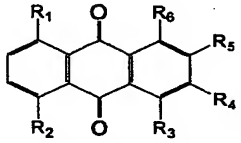
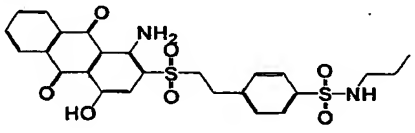
47009	# 10		2-[4-(3-Hydroxy-propyl)-piperazine-1-yl]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	369,4	C18H19N5O2S
44837	# 11		2-Ethylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	270,3	C13H10N4OS
44841	# 12		2-Dimethylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	270,3	C13H10N4OS
44843	# 13		2-Diisopropylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	326,4	C17H18N4O2S
45061	# 14		(4-Methoxy-phenylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	348,4	C18H12N4O2S
45063	# 15		N-(-Cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-acetamide	284,3	C13H8N4O2S
46472	# 16		2-Benzylamino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	332,4	C18H12N4OS
46622	# 17		2-(4-Methoxy-benzylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile	362,4	C19H14N4O2S
46626	# 18		N-(8-Cyano-7-oxo-6,7-dihydro thiazolo[4,5-f]quinoline-2-yl)-N (3-dimethylamino-propyl)-acetamide	369,4	C18H19N5O2S
46836	# 19		7-Oxo-2-(2-pyridine-2-yl-ethylamino)-6,7-dihydrothiazolo[4,5-f]quinoline 8-carbonitrile	347,4	C18H13N5OS

Table 2: Group I

EMD	No	Structure	Chemical name	Molecular weight	Empirical formula
	Molecular scaffold I-1		Basic structure: 1H-perimidine		
35222	# 1		2-(1H-Imidazole-4-yl)-1H-perimidine	234,3	C14H10N4
35361	# 2		2-Pyridine-3-yl-1H-perimidine	245,3	C16H11N3
	Molecular scaffold I-2		Basic structure: 4,5-Dihydro-pyrrolo[3,2,1-ij]quinoline-6-one		
207852	# 3		8-Fluoro-1,2-dimethyl-4,5-dihydro-pyrrolo[3,2,-ij]quinoline-6-one	233,3	C16H16FNO
	Molecular scaffold I-3		Basic structure: Tetrahydro-fluorene		
127707	# 4		2-Furan-2-yl-2,3,4,9-tetrahydro-1H-indenol[2,3-c]pyridine-3-carboxylic acid methyl ester	295,3	C18H17NO3
	Molecular scaffold I-4		Basic structure: Anthracene		
171360	# 5		7-Amino-8-[2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one	362,4	C21H18N2O4
36934	# 6		7-Amino-1,8,10a,11-tetraydroxy-10,12-dioxo-6,6a,7,10,10a,12-hexahydro-5aH-5-thia-naphthacene-9-carboxylic acid amide	404,4	C18H16N2O7S
	Molecular scaffold I-5		Basic structure: 4a, 9a-Dihydro-anthraquinone		
79809	# 7		4-[2-(1-Amino-4-hydroxy-9,10dioxo-9,10-dihydro-anthracene-2-sulfonyl)-ethyl]-N-propyl-benzenesulfonamide	528,6	C25H24N2O7S2

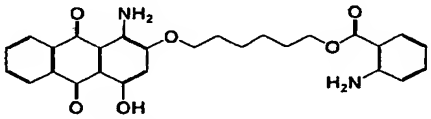
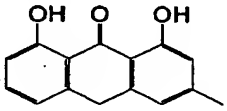
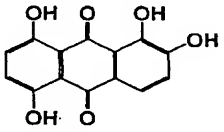
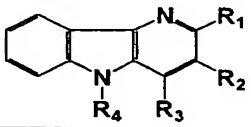
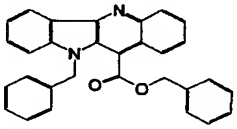
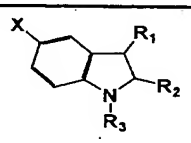
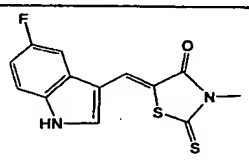
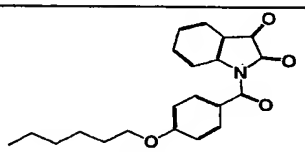
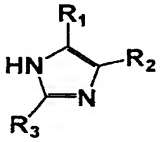
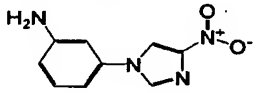
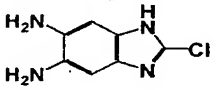
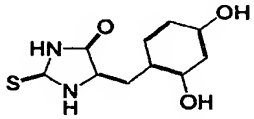
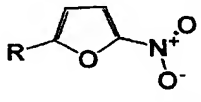
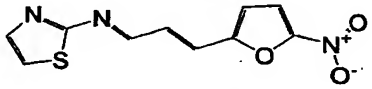
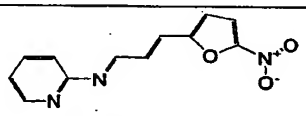
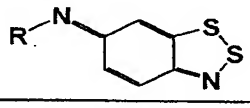
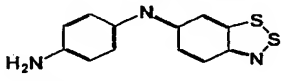
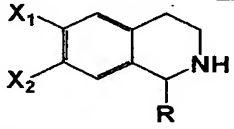
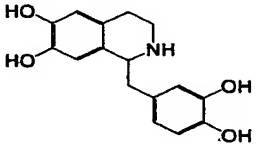
79810	# 8		2-Amino-benzoic acid 6-(1-amino-4-hydroxy-9,10-dioxo-9,10-dihydro-anthracene-2-yloxy)-hexyl ester	474,5	C27H26N2O6
171211	# 9		1,8-Dihydroxy-3-methyl-10H-anthracene-9-one	240,3	C15H12O3
19916	# 10		1,2,5,8-Tetrahydroxy-anthraquinone	272,3	C14H8O6
	Molecular scaffold 1-6		Basic structure: 10H-Indolo[3,2-b]quinoline		
84508	# 11		10-Benzyl-10H-indolo[3,2-b]quinoline-11-carboxylic acid benzyl ester	442,5	C30H22N2O2

Table 3: Group III

EMD	No	Structure	Chemical name	Molecular weight	Empirical formula
	Molecular scaffold III 1		Basic structure: 1H-Indole		
162201	# 1		5-(5-Fluoro-1H-indole-3-ylmethylene)-3-methyl-2-thioxo-thiazolidine-4-one	308,4	C14H13FN2OS2
155938	# 2		1-(4-Hexyloxy-benzoyl)-1H-indole-2,3-dione	351,4	C21H21NO4
	Molecular scaffold III 2		Basic structure: 1H-Imidazole		
127211	# 3		3-(4-Nitro-imidazole-1-yl)-phenylamine	204,19	C9H8N4O2
149571	# 4		2-Chloro-1H-benzoimidazole-5,6-diamine	182,6	C7H7ClO4
148257	# 5		5-(2,4-Dihydroxy-benzylidene) 2-thioxo-imidazolidine-4-one	236,5	C10H8N2O3S
	Leitstruktur III-3		Basic structure: 2-Nitro-furan		
91924	# 6		[3-(5-Nitro-furan-2-yl)-allylidene]-thiazole-2-yl-amine	249,2	C10H7N3O3S
91876	# 7		[3,(5-Nitro-furan-2-yl)-allylidene]-pyridine-2-yl-amine	243,2	C12H9N3O3
	Molecular scaffold III 4		Basic structure: Benzo[1,2,3]dithiazole-6-ylideneamine		
41693	# 8		N-Benzo[1,2,3]dithiazole-6-ylidene-benzene-1,4-diamine	259,3	C12H9N3S2
	Molecular scaffold III 5		Basic structure: 1,2,3,4-Tetrahydro-isoquinoline		
16797	# 9		1-(3,4-Dihydroxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline-6,7-diol	287,3	C16H17NO4

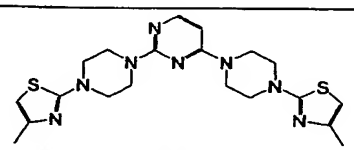
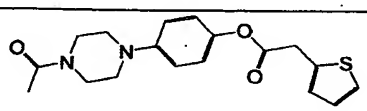
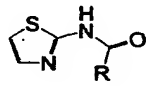
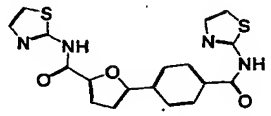
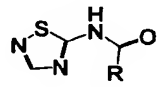
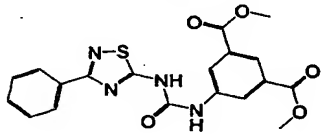
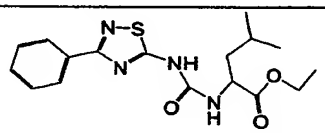
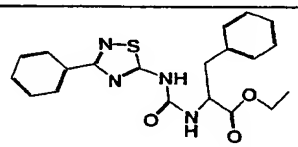
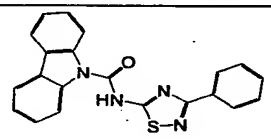
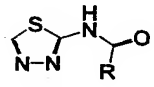
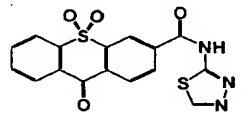
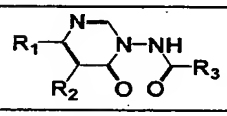
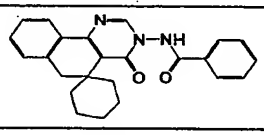
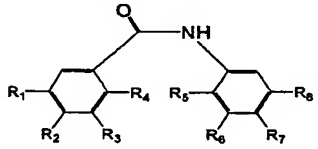
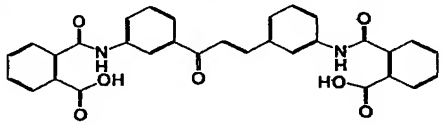
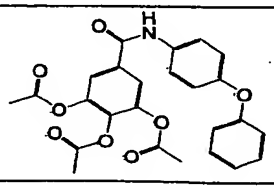
	Molecular scaffold III 6		Basic structure: Piperazine		
24445	# 10		2,4-Bis-[4-(4-methyl-thiazole-2 yl)-piperazine-1-yl]-pyrimidine	442,6	C20H26N8S2
208031	# 11		Thiophene-2-yl-acetic acid 4-(4-acetyl-piperazine-1-yl)-phenyl ester	344,4	C18H20N2O3S

Table 4: Group IV

Molecular scaffolds L1 - L6: R can be replaced by amine or aryl group or H

EMD	No	Structure	Chemical name	Molecular weight	Empirical formula
	Molecular scaffold IV-1		Basic structure: N-Thiazole-2-yl-formamide	-	-
156140	# 1		5-[4-(Thiazole-2-ylcarbamoyl)-phenyl]-furan-2-carboxylic acid thiazole-2-ylamide	396,4	C18H12N4O3S2
	Molecular scaffold IV-2		Basic structure: N-[1,2,4]Thiadiazole-5-yl-formamide	-	-
139895	# 2		5-[3-(3-Phenyl-[1,2,4]thiadiazole-5-yl)-ureido]-isophthalic acid dimethylester	412,2	C19H16N4O5S
139061	# 3		4-Methyl-2-[3-(3-phenyl-[1,2,4]thiadiazole-5-yl)-ureido]-pentanoic acid ethyl ester	362,4	C17H23N4O2S
139695	# 4		3-Phenyl-2-[3-(3-phenyl-[1,2,4]thiadiazole-5-yl)ureido]-propionic acid ethyl ester	396,5	C20H20N4O3S
139815	# 5		Carbazole-9-carboxylic acid (e-phenyl-[1,2,4]thiadiazole-5-yl)-amide	370,4	C21H14N4OS
	Molecular scaffold IV-3		Basic structure: N-[1,3,4]Thiadiazole-2-yl-formamide	-	-
126117	# 6		9,10,10-Trioxo-9,10-dihydro-10λ6-thioxanthene-3-carboxylic acid [1,3,4]thiadiazole-2-ylamide	371,4	C16H9N3O4S2
	Molecular scaffold IV-4		Basic structure: N-(6-Oxo-6H-pyrimidine-1-yl)-formamide	-	-
133081	# 7		?	385,5	C24H23N3O2
	Molecular scaffold IV-5		Basic structure: n-Phenyl-benzamide		
98228	# 8		N-[3-(3-{3-[(2-Carboxy-phenyl)-1-enecarbonyl)-amino]-phenyl}-acryloyl)-phenyl]-phthlamic acid	534,5	C31H22N2O7
118762	# 9		Acetic acid 2,6-diacetoxy-4-(4-phenoxy-phenylcarbamoyl)-phenyl ester	463,4	C25H22NO8

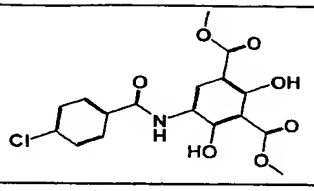
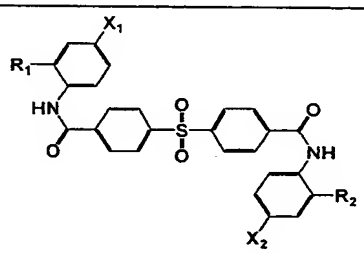
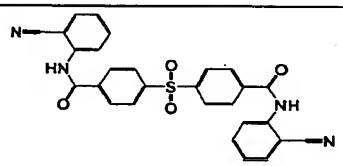
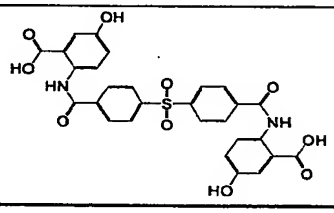
18024	# 10		5-(4-Chloro-benzoylamino)-2,4-dihydroxy-isophthalic acid dimethyl ester	379	C17H14ClNO7
	Molecular scaffold IV-6		?		
208123	# 11		2-{4-[4-(2-Cyano-phenylcarbamoyl)-benzenesulfonyl]-benzoylamino}-3-cyano-benzene	506,5	C28H18N4O4S
208125	# 12		2-{4-[4-(2-Carboxy-4-hydroxy-phenylcarbamoyl)-benzenesulfonyl]-benzoylamino}-5-hydroxy-benzoic acid	576,5	C28H20N2O10S

Table 5: Group V

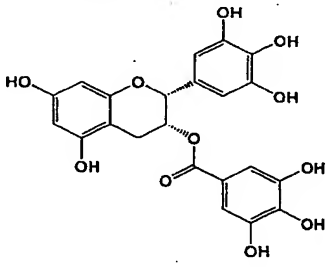
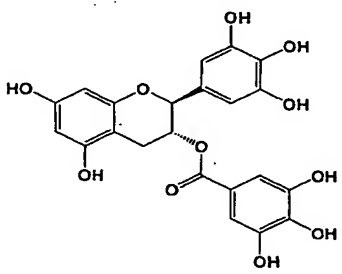
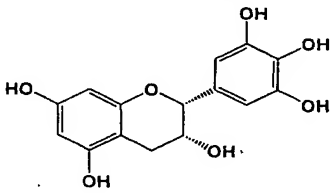
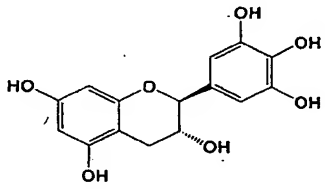
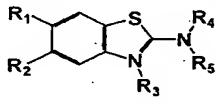
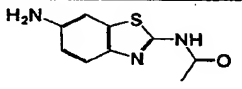
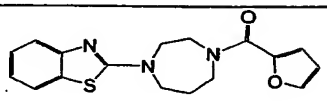
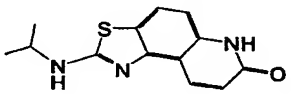
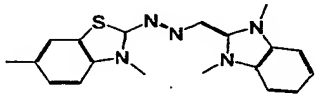
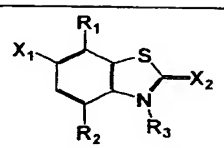
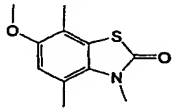
Name	Structure	Chemical name	Molecular weight	Empirical formula
EGCG		(-)-Epigallocatechin gallate	454,4	C22H18O11
GCG		(-)-Gallocatechin gallate	454,4	C22H18O11
EGC		(-)-Epigallocatechin	306,3	C15H14O7
GC		(-)-Gallocatechin	306,3	C15H14O7

Table 6: Group VI (Benzothiazoles) 54

	Name	Structure	Chemical name	Molecular weight	Empirical formula
	Molecular scaffold VI-1		Basic structure: 2-Aminobenzothiazole		
390632	# 1		N-(6-Amino-benzothiazole2-yl)-acetamide	207,3	C9H9N3OS
37821	# 2		(4-Benzothiazole-2-yl-[1,4]diazepan-1-yl)-furan-2-yl-methanone	327,4	C17H17N3O2S
46269	# 3		2-Isopropylamino-6H-thiazolo[4,5-f]quinoline-7-one	259,3	C16H13N3OS
124918	# 4		(1,3-Dimethyl-1,3-dihydro-benzoimidazole-2-ylidenemethyl)-3,6-dimethyl-2,3-dihydro-benzothiazole-2-yl)-diazene	351,5	C19H21N5S

	Molecular scaffold VI-2		Basic structure: Benzothiazole		
478931	# 5		6-Methoxy-3,4,7-trimethyl-3H-benzothiazole-2-one	223,3	C11H13NO2S

The figures show:

Figure 1: Influence of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one *in vitro* on the aggregation von mutant huntingtin and amyloid ß.

Figure 2: Examination of the effects of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one in the cell culture model of Huntington's chorea.

Figure 3: Inhibition of the aggregation of wild type $Aß_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 4: Inhibition of the aggregation of wild type $Aß_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 5: Inhibition of toxicity of extracellular wild type $Aß_{1-42}$ by the substances in mammalian cells (neuronally differentiated PC12 cells: Identification by means of MTT test) (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 6: Inhibition of the aggregation of huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 7: Inhibition of the amyloid fibril formation of huntingtin (Exon-1) (electron microscopy)

Figure 8: Inhibition of the aggregation of ataxin-3 in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 9: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 10: Inhibition of the aggregation of wild type $Aß_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 11: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 12: Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 13: Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 14: Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 15: Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 16: Binding to amyloid-beta aggregates located on a cellulose acetate membrane

Figure 17: Inhibition of the toxicity of extracellular wild type $A\beta_{1-42}$ by the substances in mammalian cells (neuronally differentiated PC12 cells: Identification by means of MTT test) (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 18: Inhibition of the aggregation of huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 19: Inhibition of the aggregation of Huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 20: Inhibition of the aggregation of ataxin-3 in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 21: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 22: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 23: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 24: Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 25: Inhibition of the aggregation of mutated huntingtin (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 26: Inhibition of the aggregation of alpha-synuclein (representation of the amyloid fibrils by means of electron microscopy)

Figure 27: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 28: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 29: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 30: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 31: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 32: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 33: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 34: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 35: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

Figure 36: Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method)

The examples illustrate the invention.

Example 1

Material and methods

For the *in vitro* experiments, the aggregation inhibiting effect of the compounds on mutant huntingtin was first examined with the help of the GST fusion protein GST-HDQ51. As in the tests described by Heiser *et al.* (2002), the protein was used for aggregation tests to which either only solvent or solvent and the chemical agent in question was added. Aliquots of these batches were examined by means of the membrane filter test and electron microscopy. By means of one of the two or both methods, an aggregation inhibiting effect of the listed compounds could be verified.

Analogously, the compounds were also examined in aggregation assays with the amyloid ß-peptide $A\beta_{1-42}$(E22Q), which is a particularly rapidly aggregating variant of amyloid ß, as well as with non-mutated (wild type) $A\beta_{1-42}$. For this purpose, the peptide was incubated at a concentration of 15 µM in a phosphate buffer with a physiological pH value of 7.4 for 42 h at 37°C and subsequently, aliquots were examined by means of the membrane filter method (Figure) or electron microscopy (Figures) as well. These tests showed that the compounds listed also effectively inhibit the aggregation of the amyloid ß-peptide *in vitro*. Cell viability measurements were carried out in neuronally differentiated PC12 cells to which beta-amyloid and the substances to be tested were added extracellularly in order to examine whether the compounds are able to reduce toxicity caused by amyloid-beta. After 48 h the viability of the cells (approximately corresponds to the number of vital cells) was measured.

The compounds were then tested in several cell culture models of polyglutamine diseases, *inter alia* Huntington's chorea. For this purpose, COS1 cells were transiently transfected with the plasmid pTL1-CAG51 already described above (Sittler, A., Walter, S., Wedemeyer, N., Hasenbank, R., Scherzinger, E., Eickhoff, H., Bates, G.P., Lehrach, H. and Wanker, E.E. (1998) *Mol Cell* **2,** 427-36) and cultivated for 44 h in the presence of solvents or the chemical agents. Subsequently, the

amount of aggregate was determined with the help of the membrane filter test as described by Heiser *et al.* (2002). The compounds described showed an aggregation inhibiting influence in the cell culture model as well (Figures) without having a toxic effect at the concentrations used. The latter could be deduced from the total amount of protein in the cell lysate (Figure 2B) which was determined with the help of cell extracts.

In addition, it was examined in this cell culture model of Huntington's chorea whether the substances tested substances can cause cell damage by initiating apoptotic processes. For this purpose, the activity of two caspases (caspases-3/ -7) was determined fluorometrically after addition of a fluorogenic substrate. The measurements showed that the compounds have positive effects on the activation of caspases (Figures).

For some compounds, a positive effect could be observed in another cell culture model of Huntington's chorea and a cell culture model of spinocerebellar ataxia (type 3). A test system based on the aggregation of an N-terminal ataxin-3 deletion construct (aa 221-360) with 71 glutamines in COS-1 cells was developed to isolate substances inhibiting the ataxin-3 aggregation. The cells were transiently transfected with the ataxin-3 expression construct and incubated in plates with 96 perforations with the added substance at 37°C in an incubator. After 40 h the cells were harvested and lysated. The lysates were denatured in the presence of 2% SDS and analyzed using the filtration method.

In order to detect the inhibiting effect of the substances on the aggregation of alpha-synuclein, the formation of amyloid fibrils was observed with the help of electron microscopy. For this purpose, the wild type protein or a mutant (A53T) was used.

Example 2

Formula I-1

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by 2-(1H-imidazole-4-yl)-1H-

perimidine, 1-ethyl-1H-perimidine, 2-pyridine-3-yl-1H-perimidine and 2-p-tolyl-1H-perimidine (see Figure 3).

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by 1,2-dimethyl-1H-perimidine, 4-(1H-perimidine-2-yl)-benzonitrile, 1H,3H-perimidine-2-thione and 3-(1H-perimidine-2-yl)-phenylamine (see Figure 4).

Inhibition of toxicity of extracellular wild type $A\beta_{1-42}$ by 3-(1H-perimidine-2-yl)-phenylamine in mammalian cells (neuronally differentiated PC12 cells): Identification by means of MTT test (quantification of SDS-insoluble aggregates by means of membrane filter method) (see Figure 5).

Inhibition of the aggregation of huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method) by (1-methyl-1H-perimidine-2-yl)-methanol (see Figure 6).

Inhibition of the amyloid fibril formation of huntingtin (Exon-1) (electron microscopy) by 2-pyridine-4-yl-2,3-dihydro-1H-perimidine (see Figure 7).

Example 3

Formula I-2:

Inhibition of the aggregation of ataxin-3 in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 8-fluoro-1,2-dimethyl-4,5-dihydro-pyrrolo[3,2,1-ij]quinoline-6-one (see Figure 8).

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 8-fluoro-1,2-dimethyl-4,5-dihydro-pyrrolo[3,2,1-ij]quinoline-6-one (see Figure 9).

Example 4

Formula I-3:

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by 2-furan-2-yl-2,3,4,9-tetrahydro-1H-indenol[2,3-c]pyridine-3-carboxylic acid methyl ester (see Figure 10).

Example 5

Formula I-4:

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 3H-phenoxazine, phenoxazin-3-one, 7-amino-1,9-dimethyl-phenoxazine-3-one, beta-amino-orcein, alpha-amino-orcein and alpha-hydroxy-orcein (see Figure 11).

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by 1,9-dimethyl-phenoxazine-3-one (see Figure 12).

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by 7-hydroxy-1,9-dimethyl-phenoxazine-3-one (see Figure 13).

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by alpha-amino-orcein (see Figure 14).

Inhibition of the aggregation of wild type $A\beta_{1-42}$ (quantification of SDS-insoluble aggregates by means of membrane filter method) by beta-hydroxy-orcein (see Figure 15).

The following – colored – substances bind directly to amyloid-beta fibrils (see Figure 16: amyloid-beta aggregates located on a cellulose acetate membrane): Alpha-amino-orcein, alpha-hydroxy-orcein, alpha-amino-orceimine, beta-hydroxy-orcein, beta-amino-orcein, beta-amino-orceimine, gamma-amino-orcein, gamma-hydroxy-orcein, gamma-amino-orceimine, phenoxazine, phenoxazone (see Figure 16).

Inhibition of the toxicity of extracellular wild type $A\beta_{1-42}$ by the substances in mammalian cells (neuronally differentiated PC12 cells: Identification by means of MTT test) (quantification of SDS-insoluble aggregates by means of membrane filter method) by alpha-amino-orcein (see Figure 17).

Example 6

In this example, the compound 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one (also referred to as # 6 in Figure 1) and its effects on the aggregation of the huntingtin protein and the amyloid ß-peptide *in vitro* as well as its effects in the cell culture model of Huntington's chorea are described.

For the *in vitro* experiments, the aggregation inhibiting effect of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one on mutant huntingtin was first examined with the help of the GST fusion protein GST-HDQ51. As in the tests described by Heiser *et al.* (2002), the protein was used for aggregation tests to which either only solvent or solvent and 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one was added. Aliquots of these batches were examined by means of the membrane filter test (Figure 1B) and electron microscopy (Figures 1E and 1F). By means of both methods, an aggregation inhibiting effect of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one could be verified.

Analogously, the compound was also examined in aggregation assays with the amyloid ß-peptide Aß1-42[E22Q] which is a particularly rapidly aggregating variant of amyloid ß. For this purpose, the peptide was incubated at a concentration of 15 µM

in a phosphate buffer with a physiological pH value of 7.4 for 42 h at 37°C and subsequently, aliquots were examined by means of the membrane filter method (Figure 1A) or electron microscopy (Figures 1C and 1D) as well. These tests showed that 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one also effectively inhibits the aggregation of the amyloid ß-peptide *in vitro*.

7-Amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one was then tested in a cell culture model of Huntington's chorea. For this purpose, COS1 cells were transiently transfected with the plasmid pTL1-CAG51 already described above (Sittler, A., Walter, S., Wedemeyer, N., Hasenbank, R., Scherzinger, E., Eickhoff, H., Bates, G.P., Lehrach, H. and Wanker, E.E. (1998) *Mol Cell* **2,** 427-36) and cultivated for 40-44 h in the presence of solvents or 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one. Subsequently, the amount of aggregate was determined with the help of the membrane filter test as described by Heiser *et al.* (2002). 7-Amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one showed an aggregation inhibiting influence in the cell culture model as well (Figure 2A) without having a toxic effect. The latter could be deduced from the total amount of protein (Figure 2B) which was determined with the help of cell extracts.

In addition, it was examined in this cell culture model of Huntington's chorea whether 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one can cause cell damage by initiating apoptotic processes. For this purpose, the activity of two caspases (caspases 3 and 7) was determined fluorometrically after addition of a fluorogenic substrate. The measurements showed that the cultivation in the presence of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one not only did not cause cell damage but, to the contrary, had an especially favorable effect on the cells since their caspase activity was reduced (Figure 2C).

This observation is in line with the observation that in the presence of 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one the total protein content was increased by almost 20% which can be interpreted as a sign for increased cell growth.

The experiments presented here using 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one as an example were also carried out analogously with the other compounds. In the case of some compounds, a positive effect could be observed in another cell culture model of Huntington's chorea and in a cell culture model of spinocerebellar ataxia (type 3).

The experiments presented here using 7-amino-8-(2,4-dihydroxy-6-methyl-phenyl)-1,9-dimethyl-phenoxazine-3-one as an example were also carried out analogously with the other compounds (see examples above and below). In the case of some compounds, a positive effect could be observed in another cell culture model of Huntington's chorea and in a cell culture model of spinocerebellar ataxia (type 3).

Example 7

Formula I-5:

Inhibition of the aggregation of huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method) by dihydroxyanthraquinone (danthron) (see Figure 18).

Example 8

Formula I-9:

Inhibition of the aggregation of huntingtin (Exon-1) (quantification of SDS-insoluble aggregates by means of membrane filter method) by chrysarobin (see Figure 19).

Example 9

Formula II-2:

The compounds were additionally tested in a stably transfected PC12 cell line. This cell line was transfected with an ecdysone-inducible plasmid whose N-terminal codes for huntingtin-Exon1 marked with GFP with 103 glutamines (Htt103Q-EGFP). The Htt103Q-EGFP expression was induced with muristerone and the cells were subsequently cultivated for 44 h in the presence of solvents or the chemical agents. Subsequently, the amount of aggregate was determined with the help of the membrane filter test as described by Heiser *et al.* (2002). Furthermore, the amount of aggregate was determined with the help of a fluorescence measurement (data not shown). The compounds described showed an aggregation inhibiting influence in the cell culture model as well (Figures) without having a toxic effect at the concentrations used. The latter could be deduced from the total amount of protein in the cell lysate (Figure 2B) which was determined with the help of cell extracts.

Inhibition of the aggregation of huntingtin (Exon-1) in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 2-amino-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 27), 2-(3-dimethylamino-propylamino)-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 28), N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-N-(3-dimethylamino-propyl)-formamide (see Figure 29), N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-acetamide (see Figure 30), N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-N-(2-dimethylamino-ethyl)-formamide (see Figure 31), N-(8-cyano-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-2-yl)-N-(2-dimethylamino-ethyl)-acetamide (see Figure 32), 7-oxo-2-(2-piperidine-1-yl-ethylamino)-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 33), 2-[4-(3-hydroxy-propyl)-piperazine-1-yl]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 34), 2-[benzyl-(2-dimethylamino-ethyl)-amino]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 35) and 2-[(2-diethylamino-ethyl)-ethyl-amino]-7-oxo-6,7-dihydro-thiazolo[4,5-f]quinoline-8-carbonitrile (see Figure 36).

Example 10

Formula III-6:

Inhibition of the aggregation of ataxin-3 in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by thiophene-2-yl-acetic acid 4-(4-acetyl-piperazine-1-yl)-phenyl ester (see Figure 20).

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by thiophene-2-yl-acetic acid 4-(4-acetyl-piperazine-1-yl)-phenyl ester (see Figure 21).

Example 11

Formula IV-1:

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 5-[4-(thiazole-2-ylcarbamoyl)-phenyl]-furan-2-carboxylic acid thiazole-2-ylamide (see Figure 22).

Example 12

Formula IV-2

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 4-methyl-2-[3-(3-phenyl-[1,2,4]thiadiazole-5-yl)-ureido]-pentanoic acid ethyl ester (see Figure 23).

Inhibition of the aggregation of huntingtin in mammalian cells (quantification of SDS-insoluble aggregates by means of membrane filter method) by 4-methyl-2-(3-phenyl-[1,2,4]thiadiazole-5-yl)-pentanoic acid ethyl ester (see Figure 24).

Example 13

Formulas V-1 to V-4:

Inhibition of the aggregation of mutated huntingtin (quantification of SDS-insoluble aggregates by means of membrane filter method) by EGCG (Epigallocatechin gallate), GCG (Gallocatechin gallate), GC (Gallocatechin) and EGC (Epigallocatechin) (see Figure 25).

Inhibition of the aggregation of alpha-synuclein (representation of the amyloid fibrils by means of electron microscopy) by EGCG (Epigallocatechin gallate), GCG (Gallocatechin gallate), GC (Gallocatechin) and EGC (Epigallocatechin) (see Figure 26).

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